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# SYMPATHETIC CONTROL OF HUMAN BLOOD VESSELS

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TO  
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## FOREWORD

The role of the sympathetic nerves in the control of the blood vessels has been the object of investigation of many physiologists from the pioneer work of Crickell Langley and Elliot in this country. In recent years interest in the nature of the chemical transmitter of the sympathetic nerves has widened the topic. It appears to us opportune to describe the sympathetic control of certain blood vessels in man and to comment on the function of the sympathetic hormones—adrenaline and noradrenaline.

This work has been written primarily on the basis of studies on the circulation in the extremities but we feel that the responses have a more general application to the function and behaviour of blood vessels in other parts of the body. We have described certain fundamental experiments in some detail in order to impress their true importance on the reader. In many aspects however omissions will be readily evident both in problems still to be solved and in observations of others on this topic. But we do not regard a review of the subject as our present task. Our object is to present the concept of the control of the blood vessels from the view point of the investigator in this special field.

It is a great pleasure to acknowledge our gratitude to Dr O G Edholm, Director of the Division of Human Physiology of the National Institute for Medical Research, who collaborated with one of us in the work described in the early chapters. Without his wise counsel and outstanding experimental skill this book would never have been written.

The investigations on sympathectomized subjects were made possible by the kindness of Mr Hedley Atkins, Miss Diana Beck, Mr P Fitzgerald, Mr Ian Frazer, Mr J B Kinmonth, Professor Sir James Leirmonth, Mr J S Loughridge, Mr Peter Martin, Mr D W C Northfield, the late Mr G R B Purce, Professor C G Rob and Sir James Paterson Ross. The experiments on fainting were begun with Professor J McMichael and Professor E P Sharpey Schafer. To all of these we express our deepest gratitude.

Once more we should like to thank all those who have given

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For permission to quote passages or reproduce figures from books and journals we express our thanks to the following: *American Journal of Physiology* Fig. 7.6 top left and right; Association for Research in Nervous and Mental Diseases Fig. 7.11; *British Medical Journal* Fig. 11.2; Cambridge University Press, quotation from Foster's *Lectures on the History of Physiology*; *Clinical Science* Figs. 4.1, 4.3 and 7.5; *Heart* Fig. Ap. 4; *Journal of Physiology*, quotation from Brodie and Russell's article and Figs. 1.2, 2.1, 2.2, 2.3, 3.2, 3.4, 3.5, 3.7, 3.8, 3.9, 4.2, 5.1, 5.6, 5.7, 6.3, 6.4, 6.5, 7.7, 8.1, 8.2, 8.3, 9.3, 10.1, 10.3, 10.4 and 12.3; *Lancet* Figs. 7.8, 7.9, 7.10, 10.6, 12.1 and 12.2; *Zeitschrift für Kreislaufforschung* Figs. 12.4 and 12.5; Macmillan Fig. 12.2 (and legend); *Pflügers Archiv* Fig. 5.10; *St Thomas's Hospital Reports* 7.2, 7.3 and 7.4; *Surgery, Gynaecology and Obstetrics* Fig. Ap. 1 (and legend). In each instance the author of the article from which the figure was borrowed has been mentioned in the legend.

Finally we are most grateful to the Editorial Committee of the Physiological Society for sponsoring the publication of this book.

H. B.  
H. J. C. S.

6th August 1952

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## CHAPTER 1

### SYMPATHETIC VASOCONSTRICTOR NERVES TO SKELETAL MUSCLE

In 1941 W. McKee Bonnar obtained the M.D. of the Queen's University of Belfast with Gold Medal for a thesis entitled

The action of the sympathetic on the blood vessels of human skeletal muscle. In this chapter with special reference to Bonnar's thesis some evidence will be given that the blood vessels of human skeletal muscle are supplied by sympathetic vasoconstrictor fibres and subjected to nervous vasoconstrictor tone.

At the time the work was done a great deal was known about the action of the sympathetic on the blood vessels in the muscles of animals. Sympathetic stimulation was generally followed by vasodilatation due to release of constrictor tone. Strong stimulation caused vasoconstriction or weak vasodilatation (Baetjer 1930, Burn 1932, Gilding 1932, Anrep, Blalock and Samman 1934, Bulbring and Burn 1935, 1937). Vasoconstrictor fibres were found in the muscles of all animals examined but vasodilator fibres in some species only (Bulbring and Burn). Very little was known about the sympathetic innervation of the vessels of human muscles. Some thought that it was constrictor and advised sympathectomy for intermittent claudication, others believed that it was dilator (Finch 1944) and others considered it to be of very little significance (Abramson, Zazec, Marras 1939, Grant and Holling 1938, Prinzmetal and Wilson 1936, Woollard and Phillips 1932). It was not concerned with vasodilatation in exercise which was caused by metabolites (Grant 1938).

Barcroft, Bonnar, Edholm and Effron (1943) noticed that warming the body caused a conspicuous increase in the blood flow in a very muscular part of the body, the forearm (Fig. 1.1 top, plethysmographic method, see Appendix). This was of nervous origin, mediated by the sympathetic, since it was abolished by sympathectomy (Fig. 1.1 bottom left). It occurred after adrenaline had been introduced into the



## 2 Sympathetic vasoconstrictor nerves to skeletal muscle

forearm skin by electrophoresis to suppress the circulation (Fig 11 bottom right Fig 12). To see if it was due to the release of sympathetic vasoconstrictor tone in the muscles the median radial and ulnar nerves the motor nerves of the forearm which would be expected to convey any sympathetic fibres to the muscles (Gilding 1932) were blocked by novocaine

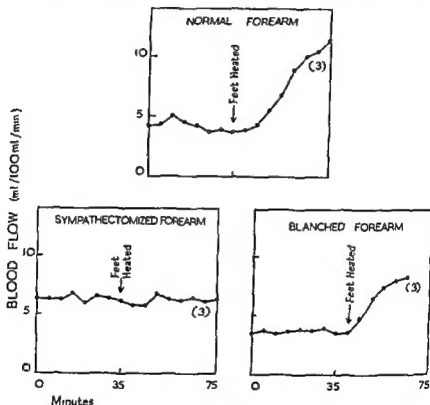


Fig 11 Experiments showing sympathetic control of the blood vessels in human skeletal muscle

Top Vasoilatation in the forearm after immersing the feet in warm water

Bottom right It can be included when the skin vessel are strongly constricted by adrenalectomy (introducing electrophoresis). It is probably due to the skin in the skeletal muscles which make up 60 per cent of the forearm tissue

Bottom left The vasoilatation abolished by sympathetic nerves. It is mediated by sympathetic fibres supply blood vessels which are present in the skeletal muscles

Averaged result Number of subjects in brackets. Bottom graph water bath temperature 3°C



#### 4 Sympathetic vasoconstrictor nerves to skeletal muscle

on one side of the body (Fig 1 3) and the circulation in the two forearms was compared. The blood flow was approximately doubled on the side of the nerve blocks (Figs 1 4 and 1 5 Table 1). Before concluding that this hyperaemia was due to release of sympathetic tone in the muscles other possibilities had to be considered.

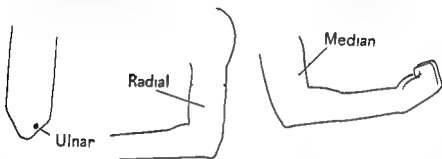


Fig 1 3 Sites for blocking the deep nerves supplying the skeletal muscle of the forearm

(1) The nerve blocks had all been done on the left forearm. It was conceivable that the normal circulation on the left side was faster than that on the right. Comparison of the blood flows on the two sides showed that the rates were approximately equal (Fig 1 4 top right).

(2) A small area of forearm skin about one third generally became anaesthetized due to unavoidable diffusion of local anaesthetic outwards to the cutaneous nerves. The sympathetic supply to this skin must have been blocked and the increase in forearm blood flow might have been due to release of tone in the cutaneous vessels. The effect of blocking the

Fig 1 4 Results showing sympathetic vasoconstrictor tone in the vessel in human skeletal muscle

*Top left* When the deep nerves (containing sympathetic) to the left forearm muscles are blocked the blood flow (circle and broken line) is about double that in the opposite normal forearm (dots and continuous line).

*Top right* This is not due to any inherent difference in the vascularity of the two sides (control 1).

*Middle* Or to unavoidable blocking of the sympathetic supply to the forearm skin (control 2).

*Bottom left* Or to removal of the mechanical hindrance of the tension on traction of the skeletal muscles (control 3).

*Bottom right* Or to passive increase in flow through the forearm skin following release of vasoconstrictor tone in the arterial tree (control 4).

*Conclusion* It must be due to the release of sympathetic vasoconstrictor tone in the blood vessels which are profusely in the skeletal muscles.

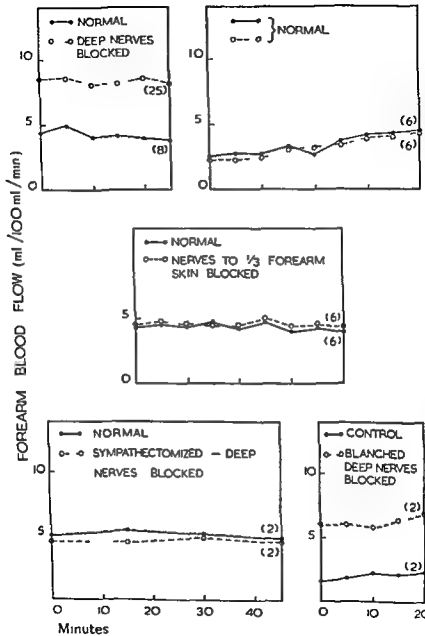


Fig 14

cutaneous nerves of the forearm on the forearm circulation was therefore tested (radial median and ulnar antebrachial nerves localized by the method of Trotter and Davies (1909)) and found to increase the forearm blood flow on the average by

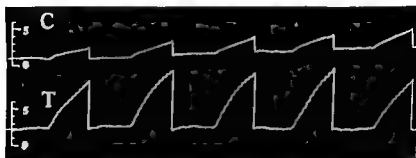


Fig 15 Simultaneous records of blood flow in the normal forearm (C) and in the opposite forearm in which the deep nerves were blocked (T). The rate of the blood flow in the nerve blocked forearm is increased owing to the release of tone in the muscle blood vessels.

Recorded at the Cambridge meeting of the Physiological Society Oct 1941  
Temperature of plethysmograph waterbath 36°C. Calibration in millilitres.  
No time tracing was made.

TABLE I

Subject	Blood flow ml per 100 ml forearm per min		Difference L - R	Percentage difference $\frac{I - R}{R} \times 100$
	Right	Left		
H B	6.9	10.3	+3.4	+49
W B	4.1	6.2	+2.1	51
H B	4.4	8	+3.6	+82
J S L	4.0	8.1	+4.1	+103
D C H	1.8	4.7	+2.9	+161
W B	2.0	5.9	+3.9	+195
A S F	3.2	9.8	+6.6	+206
Average	3.8	7.7	+3.9	+105

24 per cent. Anaesthesia of one third of the forearm skin would have increased the flow by only 8 per cent (Fig 14 middle). This could not explain the far greater increase in flow found after blocking the deep nerves (105 per cent).

(3) Blocking the deep nerves paralysed the forearm muscles

Conceivably the hyperaemia was due to abolition of muscular tone and decrease of mechanical hindrance to the circulation. However similar blocks performed on sympathectomized limbs did not increase the flow (Fig. 14 bottom left).

(4) Claude Bernard (1876) observed a rise of 20-60 mm Hg in the central end of the tibial artery of the horse following section of the cervical sympathetic. Conceivably the hyperaemia in the forearm after deep nerve block was caused by release of tone in the arterial tree beneath the deep fascia and passive increase in the cutaneous circulation. This was tested by observing the effect of deep nerve block on the forearm circulation after blanching the skin with adrenaline. Table II

TABLE II

*Protocol*

Subject O. C. L. Lying on couch. Plethysmograph diaphragms fitted to both forearms but plethysmograph not put on till later.

Time in  
Minutes

- |       |  |
|-------|--|
| 0-15  | Rest. Forearms kept warm under blankets.   |
| 15-20 | Cottonwool pad bandaged round both forearms between the diaphragms. Electrode put on each pad. Left pad soaked in adrenaline solution at room temperature. Right one soaked in saline at the same temperature. |
| 20-30 | Electrophoresis.   |
| 33-35 | Pads off. 90% of skin of left forearm intensely blanched with marked gooseflesh.   |
| 35-40 | Deep nerves blocked in the left forearm (blanche 1).   |
| 40-45 | Plethysmographs put on. Wrist cuffs put on (till 60th min.) and inflated to 200 mm Hg to prevent blood from the hands from affecting the temperature of the forearms.  |
| 45-53 | Blood flows recorded simultaneously in both forearms at 2 min. intervals. 6 sets obtained for averaging. Results: left forearm (blanched, deep nerves blocked) 2.1 ml; right forearm (normal) 0.4 ml.          |
| 53-55 | Motor movements tested. Complete paralysis of those mediated by the radial and ulnar nerves. Weakening of those mediated by the median.  |
| 55-60 | Calibration.   |
| 60-61 | Cuffs and plethysmographs taken off. Intense blanching of skin on left side.   |
| 61-64 | Circulation in both forearms arrested for 5 min. After release = flushing of the skin of the right forearm and of the left above and below but not in the blanched area.                                       |
| 7-74  | Skin temperatures taken. Left forearm (blanched, deep nerves blocked) 26.9°C. Right forearm (normal) 29.1°C. In accordance with reduction of the cutaneous blood flow on the left side.                        |

is the protocol of a typical experiment. Fig 14 (bottom right) shows the results. The blood flow was small because the fore arms were cooled to make the blanching more effective. The important point is that it was trebled in the blanched forearm in which the deep nerves had been blocked. Control experiments showed that adrenaline alone caused constriction. The vasodilatation must have been caused by the nerve blocks and it could not have been in the skin.

The whole series of experiments may be summarized as follows —After deep nerve block the blood flow in the left forearm is about double that in the right. This is not due to an inherent difference in the vascularity of the two sides (control 1) or to release of vasoconstrictor tone in the skin (control 2) or to the removal of the mechanical hindrance of tonic muscular contraction (control 3) or to a passive increase in flow through the forearm skin following release of tone deep in the arterial tree (control 4). It must be due to the release of sympathetic vasoconstrictor tone in the blood vessels in the skeletal muscles.

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## CHAPTER 2

### SYMPATHETIC VASODILATOR NERVES TO SKIN ET AL MUSCLE

The discovery of sympathetic vasodilator fibres to human muscle vessels was made accidentally during the war at the British Postgraduate Medical School (Barcroft Edholm McMichael Sharpey Schafer 1944). During an experiment on haemorrhage one of the subjects (a Friends Ambulance Unit volunteer) fainted and the tracing of the forearm blood flow shown in Fig 2 1 was recorded. The faint began soon after the twentieth minute and was fully developed by the twenty fifth. The increase in the forearm blood flow during the faint was unexpected for Lewis (1932) and Wallace and Sharpey Schafer (1941) had shown that the arterial blood pressure falls precipitously. The increase must therefore have been due to decreased vascular tone. The circulatory changes in 9 faints are shown in Fig 2 2 and the averaged blood flow results in Fig 2 3 (top left). They leave no doubt of the increase in forearm blood flow or of the decrease in the tone of the forearm vessels.

Whereabouts in the forearm was the decrease in tone? It was unlikely to be in the skin—the face went deadly pale—or in the relatively vascular bones and was probably in the muscles which make up the bulk of the forearm tissue (Abramson and Ferns 1940). This was confirmed by the observation

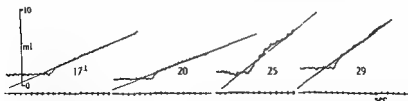
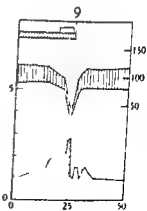
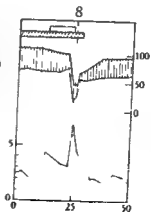
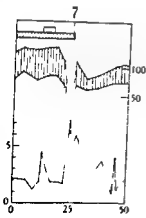
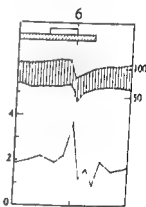
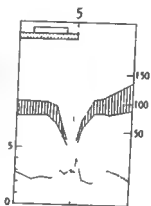
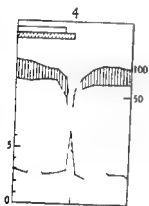
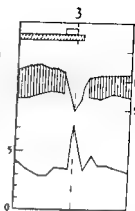
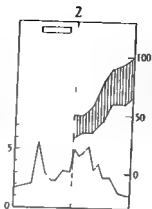
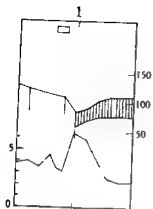


Fig. 2 1. Plethysmographic tracings of the forearm blood flow recorded by Dr O C Edholm during the first experiment on post-haemorrhagic fainting. The y-axis is forearm blood flow during the faint.

Fainting began within the 20th minute and was fully developed at the 25th minute. The initial part of the experiment are shown in Fig. 1 No. 1 (Barcroft and Edholm 1944.)





that during the faint the blood flow through the hand which contains only a small amount of muscle decreased (Fig 2 3 top right) (Barcroft and Edholm 1945)

It was now necessary to find out if possible the cause of the vasodilatation. Was it nervous or hormonal? It might have been due to the vasomotor centre (Chapter 1) or to the action of adrenaline for Grant and Pearson (1938) had shown that small doses of adrenaline caused vasodilatation in human muscle. This could be decided by experiments on sympathectomized subjects. If the vasodilatation did not occur during the faint in sympathectomized subjects it would be because the vasomotor centre could not dilate the muscle vessels. If it did occur it would be due to the action of a hormone.

The results of the experiments on the sympathectomized subjects are shown in Fig 2 3 (bottom left). During the faint forearm blood flow decreased. The increase recorded in the forearms of normal subjects must have been due to the action of the vasomotor centre.

Was the increased rate of blood flow due to release of tone in the muscle vessels or to the excitation of active vasodilatation as well? This might be settled by comparing the blood flow in normal and recently sympathectomized forearms during the faint. If it was greater in the normal one there must be active vasodilatation as well as release of constrictor tone. It would not be possible to use for this comparison the results obtained on the sympathectomized patients. Owing to the return of tone in the first few weeks after operation (see Chapter 7) the blood flow in their limbs would be far less than that in freshly sympathectomized ones. Normal forearms would have to be used in which the pathway from the vasomotor centre to the vessels was acutely interrupted by nerve blocks (see Chapter 1).

Fig 2 3 (bottom right) shows the results obtained in subjects

Fig. 2.3. Experiments showing that vasodilatation takes place in the forearm during induced post-morbid fainting. Shalel et al. (1954) used a strain-gauge method to measure blood flow in the leg (left) and arm (right) of 10 subjects. During the faint, blood flow in the arm decreased, while it increased in the leg. This indicates that the sympathetic nervous system causes vasoconstriction in the arm and vasodilatation in the leg during fainting. (Shalel et al. 1954)

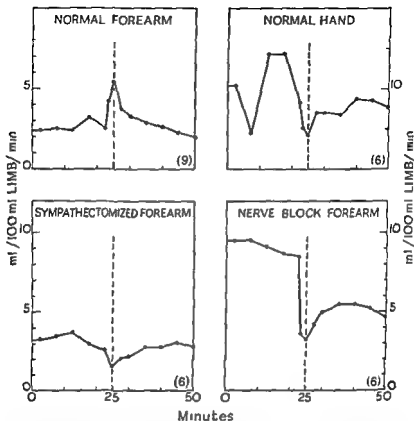


Fig. 3 Results showing that the vasodilatation in the forearm during induced posthaemorrhagic fainting is mediated by the sympathetic innervation of the skeletal muscle vessels.

Broken vertical line faint fully developed.

Top left Increase in blood flow in the normal forearm during fainting. A typical result of experiments shown in Fig. 2.

Top right Decrease in flow in the hand during fainting. The increase in flow in the forearm (top left) is therefore probably in the skeletal muscle.

Bottom left Decrease in flow in the sympathetomized forearm during fainting. The increase in flow in the normal forearm (top left) must be due to the action of the sympathetic innervation of the skeletal muscle vessels.

Bottom right Decrease in blood flow in the forearm during fainting after acute denervation of the muscles by nerve block. The results shown in this figure were used to decide whether the increase in flow in normal forearm is due merely to the reflex of sympathetic vasoconstriction or to dilatation of active vasodilatation excited by sympathetic vasodilator reflex. For further details see Fig. 4.

Averaged results. Number of subjects in brackets. (Barcroft and 12 others 1945).

fainted after deep nerve blocks. There was a large resting blood flow due to the release of vasoconstrictor tone. During the faint the flow decreased passively with the fall in arterial blood pressure. The results obtained on the normal forearms (Fig 2.3 top left) and in the forearms after deep nerve blocks

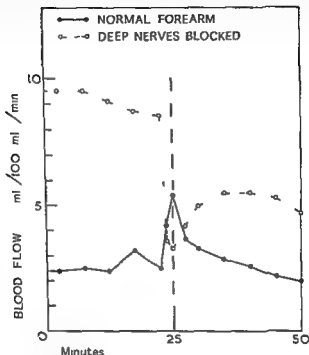


Fig. 4. Results showing that the blood flow in human muscle is supplied with sympathetic vasodilator fibres.

In this figure the results seen in Fig. 2.3 (top left and bottom right) have been superimposed.

When the faint was fully developed (broken vertical line) the blood flow in the normal forearm was considerably the greater. This is probably explained by active vasodilatation in the normal forearm excited by sympathetic vasodilator fibres.

(Fig. 2.3 bottom right) are shown superimposed in Fig. 2.4. When the faint was fully developed the blood flow in the normal forearm was considerably greater than that in the nerve blocked forearms. This must have been due to active vasodilatation mediated by sympathetic vasodilator nerve fibres.

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## CHAPTER 3

### THE ACTION OF ADRENALINE ON THE CIRCULATION IN SKELETAL MUSCLE

In the previous chapters we were concerned with the action of sympathetic nerves on the circulation in the skeletal muscles. It is convenient to turn now to the changes caused in the muscle vessels by the action of adrenaline.

The first relevant observations in man were made by Grant and Pearson in 1938. They found as shown in Fig. 3.1 that the intravenous injection of small doses of adrenaline caused a great increase in the calf blood flow as measured with the plethysmograph. However in a later paper not directly concerned with the subject, Holling (1939) pointed out that if adrenaline is given as a continuous infusion the dilatation is not maintained.

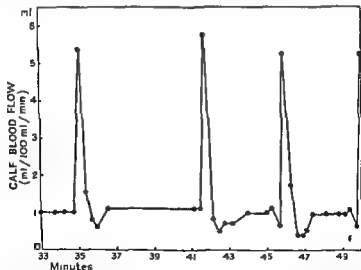


Fig. 3.1. Plethysmographic results obtained by Grant and Pearson showing vasodilatation in the calf following each of four successive intravenous injections of  $1 \mu\text{g}$  of adrenaline.

Since adrenaline always caused vasoconstriction in the skin they concluded that it must have a vasodilator action on the blood vessels in the calf muscles. (Grant and Pearson 1938)

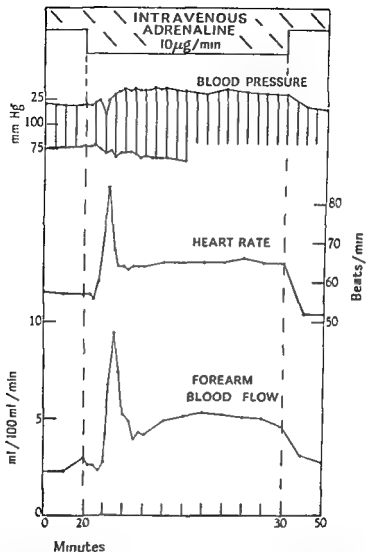


Fig. 3. Results showing, that intravenous adrenaline causes a large transient followed by a smaller sustained dilatation of the forearm.

The transient vasodilatation is due to a direct action of adrenaline on skeletal muscle vessels. The transient dilatation is due to a direct action of adrenaline on other humoral substances.

Averaged results of experiment on 6 subjects (Allen Barcroft and Fildes 1946)

Allen Barcroft and Edholm (1946) investigated the problem in some detail also using the plethysmograph. They confirmed Holling's finding observing a large transient dilatation in the forearm during intravenous infusions. This did not last longer than 2 min. after which the flow subsided to about double its initial value. Fig. 3.2 is taken from their paper.

It will be convenient now to follow first the investigations on the cause of the transient vasodilatation and then to pass on to those on the subsequent sustained vasodilatation.

### THE TRANSIENT VASODILATATION

The problem which interested Allen et al. concerned the nature of the initial transient dilatation. It was not due to emotional changes for it did not occur in experiments in which the subjects thought they were receiving adrenaline when in fact they were not. Also very small doses of adrenaline

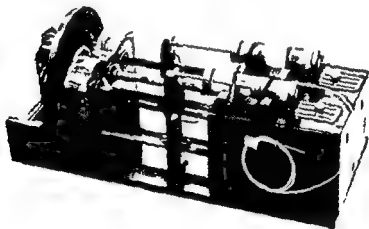


Fig. 3.3 Photograph of the infusion apparatus made by P. T. MacCallan the Radiology Workshop, St. Thomas's Hospital.

By alternate use of the syringe a continuous infusion of saline is kept up throughout an experiment at about 4 ml/min.

A second syringe is usually empty the adaptor on the tubing leading to the needle is pulled off the needle and pushed on the nozzle of the other syringe. The empty syringe is then removed, refilled and replaced.

Adrenaline added to the saline and when required. (Duff J. Physiol.)



insufficient to cause symptoms frequently caused the transient dilatation without the subjects knowledge

The saline containing the adrenaline could not have caused it for it was infused at a constant rate during the whole of every

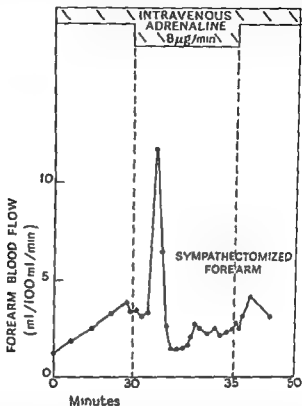


Fig 34 Result showing that intravenous adrenaline can cause a transient dilatation in the sympathectomized forearm

The vasodilatation is not mediated by the sympathetic supply to the skeletal muscle vessel (Allen Barcroft and Fildes 1940)

experiment the adrenaline was merely added to it Fig 33 shows an infusion apparatus

The effect could not be a passive one due to increase in arterial blood pressure Careful examination of the records showed that the transient increase in flow often coincided with a transient fall in the blood pressure For a simple increase in pressure to cause the increase in flow the mean arterial pressure would have to exceed 400 mm Hg

Fig 3 2 shows that there was a transient change in the heart rate rather like that in the blood flow. Atropine was given to paralyse the vagal nerve endings, adrenaline was then infused intravenously as before. The transient heart rate change was abolished but the transient vasodilatation persisted. They were not cause and effect.

Could it have been due to activity of the vasomotor centre? This seemed unlikely for if the forearm and calf blood flows were measured simultaneously the transient vasodilatation appeared in the forearm before it did in the calf. This suggested that the dilatations were due to the local action of adrenaline reaching the forearm first and the calf later. To put the matter to a more direct test intravenous infusions of adrenaline were given to subjects who had undergone sympathectomy. Fig 3 4 shows a typical result. It was clearly not dependent upon the presence of the vasomotor nerves.

Finally Allen et al showed that intra arterial adrenaline caused the transient vasodilatation (Fig 3 5). It must have been due to the direct action of adrenaline on the vessels of the limb.

The whereabouts of the transient vasodilatation was then considered. Since at the beginning of the infusion the skin always paled it was probably in the muscles. To test this observations were made on the circulation in the hand which contains relatively much less muscle and relatively much more skin than the forearm (Abramson and Ferris 1940). If the transient dilatation was in the muscles then it would be less conspicuous in the hand than in the forearm. If it was in the skin it would be more conspicuous in the hand. The results showed that it was much less evident in the hand so the dilatation in the forearm was in the muscle vessels.

The possibility that it was due to opening of the vessels in the muscles followed almost immediately by closing of those in the skin was considered and had to be rejected for the following reason. Before the beginning of the infusion the cutaneous blood flow could not exceed the total forearm blood flow i.e. about 3 ml/min (Fig 3 2). Closing the cutaneous vessels could not reduce the flow by more than that amount. Yet the decrease in flow immediately after the peak of the initial transient vasodilatation exceeded it and amounted to 5 ml/min (Fig 3 2). Therefore both the initial dilatation

and the subsequent abrupt decrease took place in the same vascular bed i.e. that in the muscles.

There is a certain amount of information relevant to the whereabouts of the vasodilatation in the muscle vessels. Dole

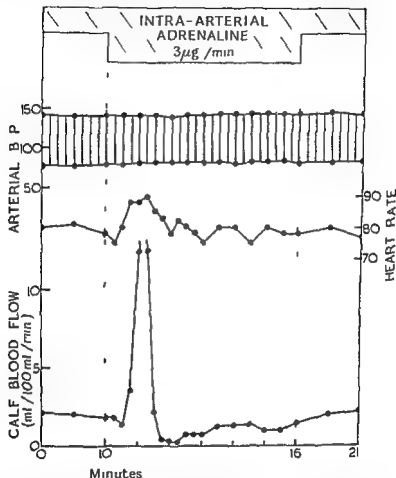


Fig. 3. Result showing that an intra-arterial infusion of adrenaline causes a transient vasodilatation in the calf.

The vasodilatation is due to a direct local action of the adrenaline in the skeletal muscle blood vessel. (Allen, Barger and L.F.B. 1946)

and Richards (1918) concluded from the analogy of their findings with acetylcholine and histamine that adrenaline caused a dilatation of capillaries but a constriction of arterioles. Hartman, Evans and Walker (1928) confirmed this.

An explanation of the transient vasodilatation in man on the basis of capillary vasodilatation followed by arteriolar constriction presents some difficulty. For example Fig 3.2 shows that at the beginning of the adrenaline infusion the blood flow increased fourfold. That is to say the resistance in the muscle circulation must have decreased to a quarter of its resting amount. If this was due to capillary vasodilatation then before the infusion at least three quarters of the total resistance

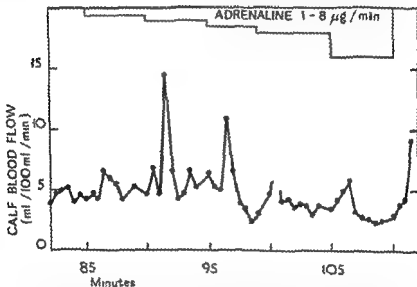


Fig 3.6 Results showing the effect on the calf blood flow of stepwise increase in the intra-arterial infusion of adrenaline from 1 to 8  $\mu\text{g}/\text{min}$ . Transient vasodilatation occurred whenever the rate of infusion was increased.

During the most rapid infusion after transient vasodilatation there was vasoconstriction.

must have been in the capillaries and must have been abolished by the arrival of the adrenaline. It is conceivable that this may be so but it has never been demonstrated and seems unlikely.

Moreover the explanation of the effect of adrenaline must account for the fact that during a continuous infusion successive increases in its rate cause successive transient vasodilatations as shown in Fig 3.6 (Allen 1946, Stead 1950, Swan 1951) and for the fact that during intravenous infusions at rates ranging

from the minimum to be effective ( $1 \mu\text{g} / \text{min}$ ) to the maximum that can be tolerated without discomfort ( $20\text{--}30 \mu\text{g} / \text{min}$ ) both dilator and constrictor phases of the transient dilatation are present the two cannot be dissociated as one would suppose might happen if the adrenaline had independent actions on two distinct parts of the vascular bed

According to Zweifach (1949) the anatomical arrangement of the vessels in skeletal muscles is more complex than is commonly supposed. He describes arterio venous anastomoses thoroughfare channels precapillary sphincters and true capillaries. If this is confirmed the interpretation of the transient vasodilatation becomes more difficult.

It may be that when adrenaline reaches the periphery it causes the momentary liberation of a vasodilator substance from the arterioles which is swept on and causes transient dilatation of the precapillary sphincters. Or it may be that it has a dual action on the arterioles—first dilatation and then constriction. Many substances have a paradoxical action—that of nicotine on the ganglia is a good example—conceivably while adrenaline begins to pass across the membrane of the smooth muscle cell normal function is temporarily inhibited and vasodilatation occurs and when equilibrium is reached the vessels return to a state of tonus governed by other factors. Either of the mechanisms if they existed could explain why successive transient vasodilatations occur in response to successive increases in the rate of a continuous infusion.

The fundamental cause of the transient vasodilator action of adrenaline is complex in the extreme and more precise statements on the causation are not at present possible.

### THE SUSTAINED VASODILATATION

At the beginning of this chapter it was shown that intra venous infusion of adrenaline caused a transient vasodilatation in the forearm followed by a smaller sustained one (Fig. 3.2). This was confirmed by Duff and Swan (1951 Table III). Similar sustained vasodilatation follows transient vasodilatation in the calf (Duff and Swan 1951 Fig. 3.7). The sustained vasodilatation is of singular interest as it probably represents the response of human muscle blood vessels to the natural physiological secretion of the suprarenal glands.

TABLE III

Changes in forearm blood flow in normal and in sympathectomized limbs during intravenous infusions of adrenaline and in normal limbs during intra arterial infusions of adrenaline Blood flow in ml/min/100 ml tissue (Duff and Swan 1951)

No	Age (yr)	Sex	Blood flow				Blood pressure		Condition	D
			A	B	B-A	B-A %	A	B		
(a) Normal forearm intravenous adrenaline 10 µg/min										
1	18	M	34	56	+22	+65	128/80	160/65	Normal	—
	19	M	34	64	+30	+88	116/85	140/80	Normal	—
3	18	M	34	77	+43	+127	135/80	165/65	Normal	—
4	19	M	9	46	+37	+410	135/80	155/70	Normal	—
5	19	M	4	3	-01	-25	135/80	150/7	Normal	—
6	19	M	17	39	+22	+130	—	—	Normal	—
7	18	M	35	54	+19	+54	134/80	160/6	Normal	—
8	33	M	19	47	+28	+147	—	—	Normal	—
9	33	M	18	42	+24	+133	—	—	Normal	—
		Av	6	51	+24	+101	/	/		
(b) Sympathectomized forearm intravenous adrenaline 10 µg/min										
1		M	31	39	+08	+26	12/76	140/76	Hypertension	6
	43	M	40	36	-04	-10	130/74	156/60	Causalgia	7
3	3	M	46	55	+09	+19	—	—	Hyperhidrosis	1
4	3	F	6	44	+38	+63	113/9	148/74	Raynaud disease	4
5	29	M	59	2	-07	-1	110/66	140/64	Causalgia	4
6	29	M	67	59	-08	-1	—	—	Causalgia	4
7		F	5	44	+39	+78	112/70	140/68	Raynaud disease	18
		Av	42	47	+05	+12	/	/		
(c) Normal forearm intra arterial adrenaline ½ µg/min.										
1	21	M	30	31	+01	+3	—	—	Normal	—
	29	M	87	38	-49	-56	—	—	Normal	—
3	21	M	19	17	-2	-10	—	—	Normal	—
4	21	M	60	63	+03	+5	—	—	Normal	—
5	20	M	80	70	-10	-12	—	—	Normal	—
6	20	M	63	60	-03	-5	—	—	Normal	—
		Av	5	47	-05	-5	/	/		

A=mean during the 4 min. prior to the start of the adrenaline infusion B=mean during the last 4 min. of the adrenaline infusion D=duration of sympathectomy in months

The explanation of the sustained vasodilatation is still unknown. The search for it has been narrowed down by Duff and Swan (1951) and by Whelan (1952).

Arterial hypertension accompanying the intravenous adrenaline does not seem to be responsible. Mean pressure is raised by only 10 mm Hg whereas the blood flow in the forearm is doubled. In individual experiments the changes in pressure and flow often seem to be quite unrelated.

The sustained vasodilatation does not appear to be due to a direct action of adrenaline on the muscle blood vessels. Duff and Swan found that during intra arterial infusions of small

amounts of adrenaline the blood flow in the calf and forearm after the initial transient vasodilatation returns to the initial level (calf  $1 \mu\text{g}/\text{min}$  forearm  $\frac{1}{8} \mu\text{g}/\text{min}$  see Fig 37 and Table III) A larger amount ( $2 \mu\text{g}/\text{min}$ ) caused constriction in the calf

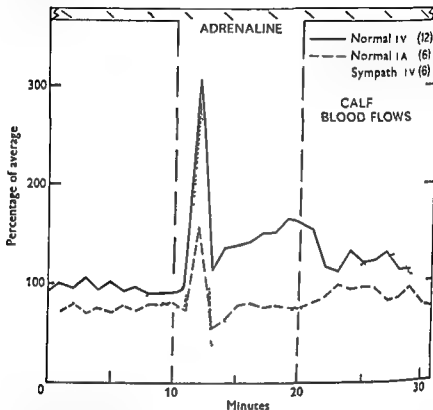


Fig 37 Result of experiments in the sustained vasodilatation in muscle caused by intravenous adrenaline

*Continuous line* Intravenous adrenaline causes transient and sustained vasodilatations in the calf ( $10 \mu\text{g}/\text{min}$ )

*Dashed line* Intra-arterial adrenaline causes transient vasodilatation only. The sustained vasodilatation cannot be due to the direct local action of adrenaline on the skeletal muscle vessels ( $1 \mu\text{g}/\text{min}$ )

*Dotted line* Intravenous adrenaline causes transient vasodilatation only in chronically sympathectomized lower limbs ( $10 \mu\text{g}/\text{min}$ )

In acutely sympathectomized lower limbs sustained vasodilatation is present (Fig 38)

Averaged results of experiment Number of ulcers in the leg (Duff and Swan 1961)

Whelan thought that the failure to find any direct vasodilator action might have been because the rates of adrenaline infusion were too great. For the intra brachial infusions Swan and Duff had used a rate of  $\frac{1}{2} \mu\text{g} / \text{min}$ . Whelan thought that the amount of adrenaline entering the forearm during an intravenous infusion at  $10 \mu\text{g} / \text{min}$  would be about  $\frac{1}{10} \mu\text{g} / \text{min}$  and might be very much less if adrenaline left the circulation or was destroyed on its way round. He therefore investigated the effect of intra brachial infusions ranging from  $\frac{1}{10}$  to  $\frac{1}{1000} \mu\text{g} / \text{min}$ . In all these after the initial transient vaso dilatation the flow was unchanged or very slightly increased. There was no sustained vasodilatation in any way comparable to that during  $10 \mu\text{g} / \text{min}$  intravenous infusions. Both Swan and Duff and Whelan are agreed that the sustained vaso dilatation cannot be due to a direct local action of the adrenaline (Whelan's estimate that not more than  $\frac{1}{10} \mu\text{g} \text{ adr} / \text{min}$  would enter the forearm during a  $10 \mu\text{g} / \text{min}$  intravenous infusion was made as follows: forearm volume 1000 ml, resting blood flow 5 ml / 100 ml forearm / min. Therefore for whole forearm 50 ml / min, cardiac output 5 litres. Therefore fraction reaching forearm is  $\frac{1}{100}$ , fraction of  $10 \mu\text{g}$  is  $\frac{1}{10} \mu\text{g}$ ).

Swan and Duff thought that the sustained vasodilatation was mediated by the sympathetic because it was unobtainable in chronically sympathectomized limbs (Fig 3.7 and Table III). However Whelan observed it in the nerve blocked forearm. His results are shown in Figs 3.8 and 3.9. Returning to the sympathectomized limb he showed that the sustained vaso dilatation was present a few hours after operation but that it grew less as hours passed between operation and the time of testing (changes in other vascular responses following sympathectomy are described in Chapter 7). This explained why Duff and Swan had not been able to find it. The results of Whelan's experiments on one of his three sympathectomized subjects are shown in Figs 3.10. It appears then that the sustained vasodilatation is definitely not mediated by the sympathetic.

The only other explanation left for it is that it is due to the direct action on the muscle blood vessels of some humoral substance other than adrenaline. This substance might be formed



from adrenaline itself during its passage from the venous to the arterial side or it might be released by adrenaline in some other part of the body. Staub (1946) found that intravenous infusion of adrenaline released histamine but Mongar and Whelan (1952) have not been able to confirm this. The sus

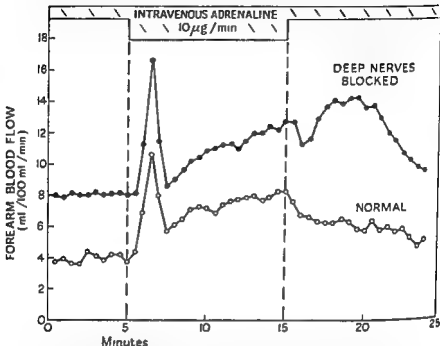


Fig 3.8 Results of experiments on the sustained vasodilatation in muscle caused by intravenous adrenaline

Owing to the release of vasoconstrictor tone resting blood flow in the nerve blocked forearm is about doubled. Apart from the difference in the general levels the behaviour of the blood flows during the adrenaline infusion looked very much alike. For better comparison the blood flows have been graphed in Fig. 3.9 after subtraction of the respective resting rates.

Averaged result of 10 infusions on 6 subjects. Healthy men aged 17-27, temperature 36.3°C. (Whelan 1952)

tained vasodilatation is not likely to be due to the release of histamine. At present the nature of this substance remains unknown.

Before leaving the subject of adrenaline and the blood flow in human muscles mention must be made of a curious response which Whelan (1952) described and which is seen when the sympathetic supply is blocked or severed. After stopping an

intravenous adrenaline infusion the blood flow instead of gradually subsiding to the resting level subsides for a short time and then shows a well marked secondary increase. This is seen in the nerve blocked forearm in Figs 38 and 39 in the acutely sympathectomized forearm in Fig 310 though not 7 hours after operation in this subject and in the chronically sympathectomized calf in Fig 37. It was recorded in a forearm which had been completely denervated by avulsion

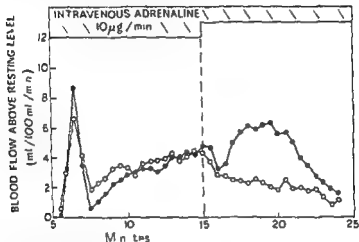


Fig 30 Experiment in the sustained vasodilatation in man caused by intravenous adrenaline

Replotted in Fig 38 graphed after subtraction of the respective resting blood flow

Transient vasodilatation was followed by sustained vasodilatation in both normal and nerve blocked forearms

The sustained vasodilatation cannot be mediated by the sympathetic nerve supply to the skeletal muscle vessels (Whelan 1952)

of the brachial plexus (Whelan 1952). Its significance is not yet known

Finally it is of interest to compare the action of adrenaline on human muscle vessels with its action on those of the cat. In the animal muscle blood flow can be recorded by more direct and satisfying methods. In studies of muscle blood flow in the intact cat however adrenaline has usually been given by intravenous injection. The observed blood flow changes have therefore been limited to those which correspond in time to the transient vasodilatation in man

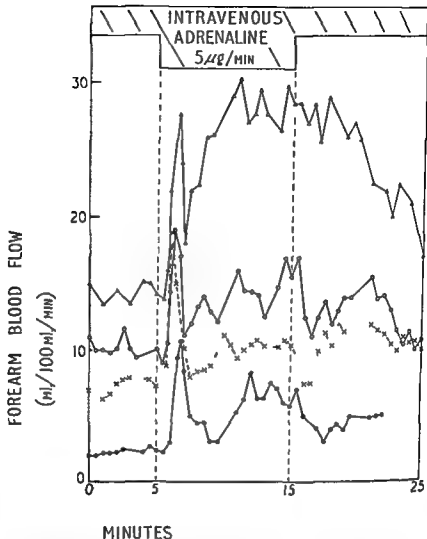


Fig 3.10 Experiments on the sustained vasodilatation caused by intravenous adrenaline

Results showing the effect of intravenous adrenaline on the forearm blood flow 2 days before (dots) and 17 hours (triangles) 24 hours (circles) and 14 days (crosses) after sympathectomy

Transient and sustained vasodilatation are conspicuous in the acutely sympathectomized limb (triangles)

The sustained vasodilatation cannot be mediated by the sympathetic nerve supply to the muscle vessel

After sympathectomy all groups pass the sustained vasodilatation down the It is also not in chronically sympathectomized limbs (Fig 3.7) (Welman 1953)

In this respect there is good agreement between the findings in the two species. Hoskins, Gunning and Berry (1916) and Gruber (1929) found that small intravenous doses of adrenaline caused active vasodilatation in feline muscle and Clark (1933) and Folkow, Frost and Uvnas (1948) showed by intra arterial injection that this was by virtue of its direct action on the muscle vessels.

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## CHAPTER 4

### THE ACTION OF NORADRENALINE ON THE CIRCULATION IN SKELETAL MUSCLE

In 1910 Barger and Dale observed that the substance we now call noradrenaline caused responses more like those of sympathetic nerve stimulation than did adrenaline. The suggestion by Bacq (1934) that noradrenaline might in fact be the mediator of excitatory sympathetic nerve impulses was not finally accepted until 1946 when von Euler identified it in extracts of organs and nerves. His discovery was the starting point of numerous investigations on its action in different organs. In this chapter we shall be concerned with its effect on the circulation in human muscle which as we shall see differs from that of adrenaline.

The first observations in man on the effect of noradrenaline on the blood flow in muscle were communicated to the Annual Meeting of the American Physiological Society at Detroit in 1949 by Duncanson, Stewart and Edholm. An abstract of their paper appeared in the *Federation Proceedings* of the same year. They found that intravenous infusions caused a slight decrease in forearm blood flow. Their finding was later confirmed both in the forearm and calf (Swan 1949, Barcroft and Konzett 1949, de Ligny, Greenfield, McCorry and Whelan 1950, Barnett, Blacket, Depoorter, Sanderson and Wilson 1950). Fig. 4.1 is from the paper by the last named authors. Although Barcroft and Konzett did not observe any initial transient vasodilatation during intravenous infusions at  $10 \mu\text{g/min}$ , a small one often occurs at the beginning of  $20 \mu\text{g/min}$  infusions after which the blood flow in the forearm returns to about the resting rate (Whelan and Young 1952).

Owing to the presence of both skin and muscle in the plethysmograph and to the fact that noradrenaline constricts cutaneous vessels as is evidenced by pallor of the skin, it is difficult to tell with assurance from the experiments just described whether on the average it caused any change in the calibre of the muscle vessels.

Barcroft and Konzett (1949) and Swan (1951) investigated the direct action of noradrenaline on the circulation in the calf. Fig. 4.2 shows at the top the results of short intra-arterial infusions. In all cases L noradrenaline caused a simple decrease in the calf blood flow; in some the flow was reduced by 75 per cent. Since skin forms only a small proportion of

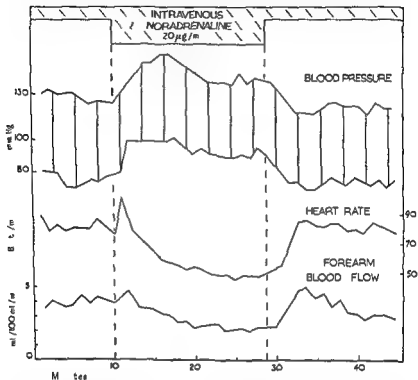


Fig. 4.1 Results showing the action of an intravenous infusion of noradrenaline on the forearm blood flow (Barnett, Blacket, Depoorter, Sande and Wilson, 1950)

the calf they thought it reasonable to conclude that it must have had a direct constrictor action on the muscle vessels.

We must now briefly compare the actions of adrenaline and noradrenaline. The most striking difference is the absence of the transient vasodilatation in the calf during intra-arterial infusions of noradrenaline. Fig. 4.2 shows clearly that the transient vasodilatation only occurs with adrenaline. Barcroft

and Konzett (1949b) found that the transient vasodilatation also occurred with isopropyl noradrenaline which has two methyl groups

It is of some interest too to compare the actions of the two substances from the point of view of deciding which of

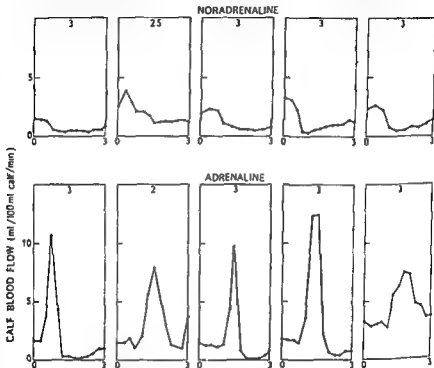


Fig. 4. Results showing the action of intra arterial noradrenaline on the circulation in human muscle.

Absence of the transient vasodilatation during intra arterial noradrenaline. Since the skin forms only a small proportion of the calf and noradrenaline reduced the calf blood flow by as much as 75 per cent it is reasonable to suppose that it had a direct vasoconstrictor action on the muscle blood vessels.

The figure under the top margin of each diagram is the rate of infusion into the femoral artery in  $\mu\text{g}/\text{min}$ . Air-filled plethysmograph (Barcroft and Konzett 1949).

them is likely to be the transmitter at the sympathetic vasoconstrictor nerve endings. The following points are relevant.

1. Noradrenaline causes simple vasoconstriction. This action is manifest during intrafemoral arterial infusions at as low a rate as  $0.5 \mu\text{g}$  per minute (Swan 1951).

- 2 The local action of adrenaline depends upon the rate of infusion. In the calf rates of  $1 \mu\text{g}$  per minute cause transient vasodilatation with a return of the blood flow to approximately the initial level. Only when the adrenaline enters the femoral artery at a greater rate does constriction take place (see Chapter 3 Table III)

On the by no means certain supposition that the effects of intra arterial infusions are comparable with those of continuous liberation at nerve endings we can speculate on the probable transmitter substance. If it were adrenaline a vasodilatation would have to precede any vasoconstriction, also considerable amounts of adrenaline would have to be liberated to cause vasoconstriction. This would not seem to be the most economical way to cause constriction. In contrast noradrenaline in very small doses causes constriction without any vasodilatation and it appears very much more likely that this substance is the mediator of the sympathetic nerve impulses to the muscle vessels.

Now let us consider the effect of a circulating mediator in distinction to that liberated at the nerve endings. It is unlikely that in natural conditions the circulation would contain only adrenaline or only noradrenaline, a mixture of very small amounts of both would be expected. The question of which of them in a mixture will have the predominant action was one which interested de Ligny, Greenfield, McCorry and Whelan (1950). They recorded the blood flow in six subjects during intravenous infusions of mixtures at the rate of  $8-10 \mu\text{g}$  per minute lasting for 5 minutes. Fig. 4.3 shows the averaged results. Beginning at the top on the left the noradrenaline contents of the mixtures in the six groups of experiments were 18, 33, 53, 75, 89 and 100 per cent. The figure shows that the effect of adrenaline predominated in mixtures containing as much as 75 per cent noradrenaline. This indicates that it is likely that noradrenaline predominates overwhelmingly at the nerve endings.

In conclusion there appears to be a difference in the action of intravenous noradrenaline in man and the cat. We have seen that in man intravenous infusions usually cause vasoconstriction in the forearm and calf (Fig. 4.1) however intravenous injections cause vasodilatation in the cat's leg. The



observations on the cat were carefully made by Meier (Cross and Eichenberger (1949) and by Cobbold and Vass (1952) Cobbold and Vass have shown that this vasodilatation is in the vessels supplying leg muscles and that it is only transient for in intravenous infusions it soon gives place to sustained constriction. The initial vasodilatation appears to be due to the

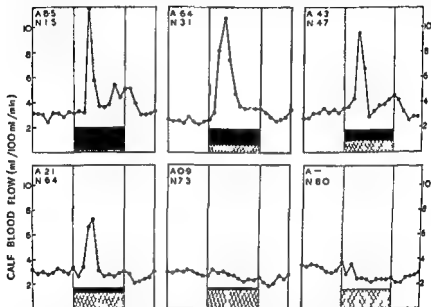


Fig. 4.3. Results showing the effect on the calf blood flow of intravenous infusions of adrenaline noradrenaline mixture containing 18, 37, 57, 77, 89 and 100 per cent noradrenaline respectively.

The transient vasodilator action of adrenaline was completely till the proportion of noradrenaline was more than 50 per cent.

Averaged result of six experiments. — adrenaline. Black rectangle noradrenaline. Hat head rectangle noradrenaline (to large credit). (McCorry and Whelan 1950).

abrupt rise in blood pressure and the subsequent constriction to the more gradual development of the constrictor action of noradrenaline on the muscle vessels. The prevention of the rise in blood pressure by a compensator abolishes the initial vasodilatation and only the subsequent constriction is seen.

In the cat as in man in all effective intra-arterial doses it has a direct vasoconstrictor action upon the muscle vessels (Cross 1949; Folkow, Frost and Uvnäs 1948).

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## CHAPTER 5

### THE CIRCULATION IN SKELETAL MUSCLE DURING EXERCISE

It is generally believed that sympathetic nerves and hormones perform important functions during stress. Their action upon the circulation in active muscle is therefore of special interest. But before discussing this it will be convenient to describe some experiments on the effect of exercise on muscle blood flow. These can be divided into two groups—those on the effect of sustained and those on the effect of rhythmic contraction.

#### SUSTAINED CONTRACTION

In 1877(a, b) Gaskell established by experiments on the dog and frog that the two most important vascular changes taking place in skeletal muscle during sustained contraction are vasodilatation and opposed to this mechanical compression. Later the relative importance of the vasodilatation and of the compression became the subject of an interesting controversy between Anrep's and Reiss's laboratories.

In man the existence of these factors had been recognized (Lundhard 1920a, b) but there was some difference of opinion as to their significance. Dolgin and Lehmann (1930) compared the times for which graded strengths of hand grip could be maintained with and without previous circulatory arrest in the upper arm. The duration of the weak grips was shortened by the arrest but that of the strong ones was not affected. They concluded that in strong grips the circulation had been arrested in the muscles. Vandell Henderson and his colleagues (1936) studied the effect of contraction of the calf muscles on the intramuscular pressure as recorded by a needle and water manometer. As strong contractions only caused a very small rise in intramuscular pressure they concluded that there could not be much resistance to the blood flow. Grant (1938) used the plethysmograph to record the changes in forearm blood flow during strong hand grips. He found a slight rise in flow during the contraction and a large one immediately after. He con-

cluded that vasodilatation occurred during sustained contraction but was restricted

Barcroft and Millen (1939) also studied the behaviour of the blood flow during sustained contraction. The principle of their method was as follows. Muscle temperature was recorded thermoelectrically. By immersing a limb in hot or cold water for an hour or more a constant difference in temperature could be achieved between a muscle and the blood entering it (at approximately body temperature). Sustained contraction was then performed. Hyperaemia could be inferred if hot muscle cooled and if cold muscle became warmer and if these temperature changes were abolished by previous circulatory arrest.

The muscles used were those in the calf of the leg. Details of the self retaining thermojunction and of its insertion into the calf muscles will be found in the original paper. Four different strengths of contraction were studied, namely 0.05, 0.1, 0.2 and 0.3 maximal. (According to Weber (1846), Koster (1868), Hermann (1896) and Peys (1915) the limiting load on the ball of the foot is about 225 kg and the pull on the Achilles tendon about 675 kg—more than half a ton.) To perform any one of the three weaker contractions the subject sat with one leg in a waterbath (a dustbin) and keeping his knee straight exerted a steady pressure with the ball of the foot on a stirrup attached to a suitably weighted lever. To perform the strongest, the 0.3 maximal, he stood on tiptoe with the knee straight on the leg in the waterbath. The two strongest contractions and all the contractions performed during previous circulatory arrest in the thigh were maintained till discomfort became intolerable. The two weaker ones were given up after a quarter and half an hour respectively and no acute discomfort was felt.

The results obtained in the weakest contraction are shown in Fig. 5.1. The upper curve on the left hand side shows that the temperature of the warmed muscle fell during exercise; the curve immediately below it shows that the temperature of the cooled muscle rose. It tended to approach the temperature of the blood entering it. This suggested hyperaemia. The results obtained when the exercises were performed during circulatory arrest are shown on the right hand side. They were quite different: there was a slight rise in the temperature of

both the warmed and the cooled muscle which could have been due to metabolic heat production. The convergence of the temperature towards body temperature observed when the circulation was free was not seen and must have been due to hyperemia.

In this experiment the exercise performed with free circulation lasted half an hour and could have been kept up for longer.

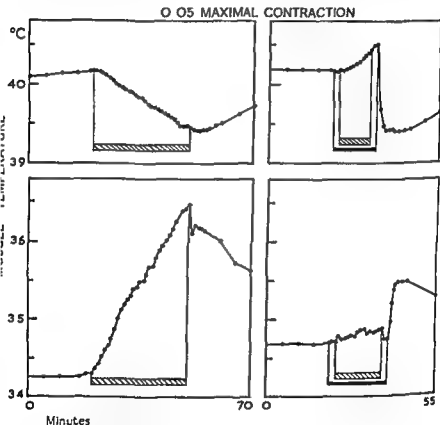


Fig. 1. Result showing that weak sustained contraction of the human gastrocnemius skeletal muscle is accompanied by hyperemia.

Upper curve: Waterbath temperature 4°C. Left muscle.

Lower curve: Waterbath temperature 3°C. Right muscle.

Hatched rectangle: 0.05 maximal contraction.

Self rectangle: 1.0 maximal contraction.

Left: During exercise the temperature fell from 1.0°C to 0.5°C.

Right: Confirmed by also the temperature changes during rest.

performed with arrested circulation.

# O 1 MAXIMAL CONTRACTION

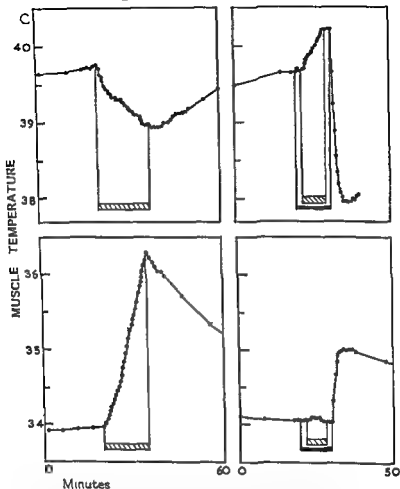


Fig. 1. Results showing that weak sustained contraction of the human  
gastrocnemius muscle is accompanied by hyperaemia.  
Upper curve: Waterbath temperature 4°C (hot muscle).  
Lower curve: Waterbath temperature 37°C (cold muscle).  
Hatched rectangle: 0-25 min, maximal contraction.  
Solid rectangle: 25-35 min, contraction arrested in the thigh.  
Left: During exercise the temperature of the muscle approaches blood  
temperature. This could have been due to hyperaemia.  
Right: Confirmation by absence of the temperature changes during exercise  
performed with arrested circulation.

When done with the circulation arrested however it had to be stopped after about 10 minutes because of unendurable discomfort. The absence of fatigue in the free circulation experiment was consistent with the conclusion that the muscle was receiving an adequate supply of blood.

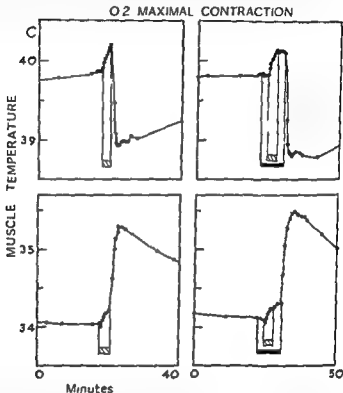


Fig. 53. Result showing that strong sustained contraction of the gastrocnemius soleus muscle is ischaemic.

Upper curve: Waterbath temperature 40°C hot muscle.

Lower curve: Waterbath temperature 30°C cold muscle.

Hatched rectangle: 0.5 maximal contraction.

Solid rectangle: circulation arrested in the thigh.

During exercise the temperature of both hot and cold muscle increased when circulation free and when it was arrested. There could not have been any appreciable blood flow through the muscle in either case.

Hyperemia also of functional significance occurred too during the 0.1 maximal contractions as will be seen from Fig. 52.

The behaviour of the circulation during the stronger contractions was altogether different. Fig. 53 shows the results

of the 0.2 maximal one. During contraction the temperature of both hot and cold muscle increased. In the absence of any sign of approximation of the temperature of the hot muscle to that of the blood it was difficult to believe that there could have been hyperaemia. Indeed the striking similarity between the temperature changes recorded while the circulation was free and those obtained during circulatory arrest strongly suggested that there could have been no circulation in either case. This could easily be explained on the grounds that the intramuscular tension had overcome the arterial blood pressure and occluded the vessels supplying the muscle. Moreover the duration of the exercise performed with free circulation and maintained for as long as possible was no longer than that in the corresponding circulatory arrest experiment. Such a result would be expected if there was no circulation through the muscle in either case.

The temperature changes after relaxation are also instructive. Fig. 5.3 shows that the temperatures of the hot and of the cold muscle changed abruptly in the direction of that of the blood. This and the delay of similar temperature changes in the circulatory arrest experiment till after the circulation had been released signifies that they were caused by marked hyperaemia. Marked hyperaemia would be expected after release of the circulation to potentially widely dilated vessels.

The results of the strongest contraction, the 0.3 maximal tiptoe standing on one leg shown in Fig. 5.4 were similar, as also was the inference that mechanical compression had arrested the circulation through potentially dilated muscle vessels.

A number of interesting points need discussion. Perhaps the most striking finding is the suddenness of the change from hyperaemia to ischaemia with increasing strength of contraction. After relaxation of the 0.1 maximal contraction the blood flow apparently began to subside almost at once: there was no evidence of the removal of any mechanical obstruction. Yet a 10 per cent increase in the strength of contraction changed the whole picture to one of ischaemia. On the one hand the exercise was given up voluntarily after a quarter of an hour and on the other it became intolerable in less than 5 minutes. It seems that the circulation through the calf muscle must have been very free below a critical strength of



contraction (between 0.1 and 0.2 maximal) and nearly or quite obstructed above the critical point.

Murschak (1931) found that strenuous contraction of the forearm muscles could obliterate the radial pulse. This suggests that ischaemia of the calf muscles could conceivably have been due to nipping of the main artery or vein. This would reconcile Henderson's (1936) finding of low intramuscular

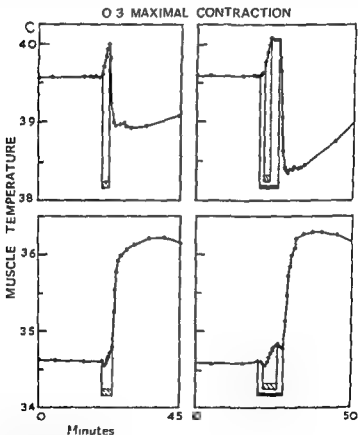


Fig. 54. Results showing that strong sustained contraction of the gastrocnemius muscle is ischaemic.

Upper curve: Waterbath temperature 4°C. Left muscle.

Lower curve: Waterbath temperature 36°C. Right muscle.

Hatched rectangle: to maximal contraction.

Solid rectangle: circulation arrested (although

During exercise the temperature of both feet and calf muscle increased when circulation was free and when it was arrested. There could not have been any appreciable blood flow through the muscle in either case.

pressure with our finding of ischaemia. It would be interesting to repeat his experiment.

It will be remembered that Crant (1938) concluded that strong sustained contraction of the forearm muscles did not prevent hyperaemia but restricted it. This was because there was a slight increase in forearm blood flow during contraction and a large increase after. There may have been a small increase in flow not shown by our method during the two strongest contractions. Another interpretation of Crant's results seems possible. During contraction there may have been ischaemia in most muscles and hyperaemia in a few. The hyperaemia might account for the small increase in flow found during the contraction. After relaxation the rush of blood through the previously ischaemic muscles could explain the conspicuous increase in flow.

It is interesting to recall that Gaskell (1877a) found that the blood flow gradually increased during tetanic stimulation of the dog's extensor muscles. Similar results have been obtained for the dog's gastrocnemius even during strong stimulation (Pein, Mertens and Schneider 1935; Kramer and Quensel 1937; Bulbring and Burn 1939). The increase was manifest after a minute's contraction. But there was no sign of this during our two stronger contractions which lasted still longer. This is probably explained by the fact that the dog's muscle may have been contracting weakly even though strongly stimulated. The importance of the tension developed in the muscle does not seem to have been appreciated. Kramer and Quensel do not mention the strength of their contractions. Rein et al. apparently tied the Achilles tendon to a 1 kg weight so that the tension developed could not have exceeded that amount. Bulbring and Burn recorded tensions of about 18 kg but these soon fell to 5 kg. Yet the maximum strength of contraction of the cat's gastrocnemius is 12.5 kg (Eccles and Sherrington 1930) and by analogy that of the dog should be about 3 kg. The reason why strong stimulation apparently elicited weak contraction in the dog is not clear.

#### THE MUSCLE PUMP

Before discussing the behaviour of the blood flow through rhythmically contracting muscle a few words must be said on

the subject of the muscle pump. Its action in man has been demonstrated by Smirk (1936) who recorded the pressure in a vein in the dorsum of the foot of a subject standing upright. Marked fall in pressure occurred when the subject raised and lowered his heels rhythmically due to emptying of the leg veins by the pumping action of the muscles. Further interesting work along these lines has appeared by Pollack Taylor Myers and Wood (1949) and by Walker and Longland (1950).

The action of the muscle pump can very easily be shown with the plethysmograph (Barcroft and Dornhorst 1949). Fig. 5.5 is from an experiment in which calf volume was

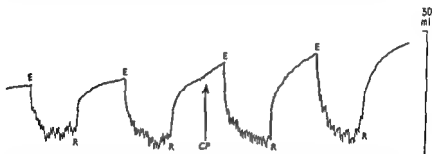


Fig. 5.5. Plethysmographic record of the volume of the calf of leg. Shrinkage denoted by downward movement of writing point.

Results showing shrinkage in calf volume during rhythmic exercise due to the action of the muscle pump.

E pedal pressed down once a second for 10 sec. R rest for 10 sec. CP cuff just above knee inflated to 90 mm Hg till end of recording. (Barcroft and Dornhorst 1948.)

recorded with the plethysmograph in a subject lying down. Periods of 10 sec. of flexion and extension of the foot alternated with periods of 10 sec. rest. During exercise pressure was exerted about once a second to the sound of a metronome with the ball of the foot on a suitably weighted pedal. Calf volume decreased at the beginning of the exercise as the blood in the veins was pumped out (Fig. 5.5). Increase took place at the beginning of each rest period as they refilled. The muscle pump has considerable power. When the venous pressure was raised to 90 mm Hg by inflation of a cuff above the knee the volume of the calf still shrank at the beginning of exercises. The contractions had forced the blood out under the cuff.

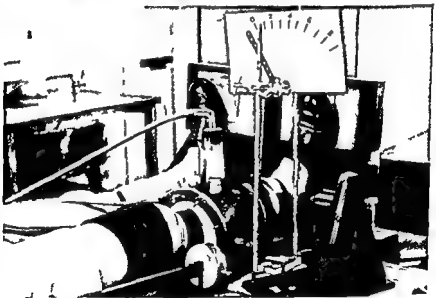
## RHYTHMIC CONTRACTION

The experiments on static contraction suggest that there would be free hyperemia in muscle during gentle rhythmic contractions. During strong ones however an intermittent flow would be expected: stasis during contraction and free flow through widely dilated vessels during relaxation. This had not been studied plethysmographically in man as it had been assumed that the to and fro movements of the muscles would interfere with recording. Thanks to the ingenuity of Dr A. C. Dornhorst it has now been done. Details of the method are given in the original paper (Barcroft and Dornhorst 1949b) and shown in Fig. 5.6. Calf volume was recorded with the plethysmograph in the supine subject as in the previous experiment on the muscle pump. The subject pressed the pedal once a second to the sound of a metronome, relaxing as completely as possible after each contraction. After the initial pump out of the venous blood the record usually showed very even up and down movements of the recorder due to the to and fro movement of the calf muscles. This may be seen in Fig. 5.7. Inflation of the thigh cuff to a pressure of about 90 mm Hg was usually followed by a regular upward trend of the oscillations from which the inflow could easily be estimated. However this was only the apparent inflow for some blood was usually forced out under the cuff by the muscle pump. To estimate the rate of blood loss the inflow was arrested by digital compression of the femoral artery in the groin. There was usually a regular downward trend of the oscillations from which the outflow could easily be estimated (Fig. 5.7). This figure was added to the apparent inflow. To see whether arterial compression had succeeded in arresting the inflow the subject then stopped exercise. Escape of blood from the calf was prevented by the venous occlusion cuff. If the inflow had ceased the recorder drew a horizontal straight line. In some subjects though there were no pulsations the line sloped gently upwards due to unavoidable inflow from collateral vessels. A small allowance was made for this in the calculation.

Fig. 5.8 shows the blood flow results obtained before, during and after six minutes of strong rhythmic exercise. The blood



(A)



(B)

Fig 56 Apparatus used in the experiment on the flow of blood in the calf during rhythmic exercise

The plethysmographic cuff is a counterpoise weight (4) a reflecting cuff on the lower part of the thigh ankle cuff for arresting the circulation in the foot heels resting on fixed supports feet on pedals horizontal bars at right angles to pedals each is pivoted separately where pedal and joint weights on bars for adjusting work done pointer actuated by movement of pedal and bar on right side (B) stops at heel end of bar one foot taking weight off pedal during relaxation the other to prevent movement of pointer beyond end of calf (4) metronome (B) straps supporting subject's shoulders (4) control bar at end of kymograph table (4) The subject is lying at the pointer (Barcroft and Doolittle 1941)

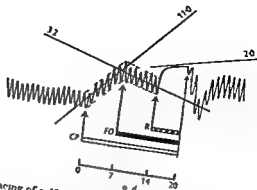


Fig 7 Tracing of calf volume changes during rhythmic exercise showing procedure for determining the exercise flow. At CP a collecting pressure of 10 mm Hg was applied. 7 s later at FO the femoral artery was occluded. After a further 7 sec at R the subject relaxed for 8 sec (Barcroft and Dornhorst 1949)

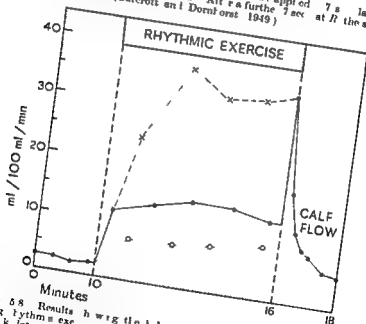


Fig 8 Results showing the effect of rhythmic exercise on calf flow. The solid line represents calf flow and the dashed line with 'x' markers represents pulmonary blood flow. The graph shows that calf flow increases during rhythmic exercise and then decreases during relaxation. Pulmonary blood flow also increases during rhythmic exercise and then decreases during relaxation. The graph is labeled with 'RHYTHMIC EXERCISE', 'RELAXATION', and 'RAPID BLOOD FLOW'.

flow increased both during the exercise and immediately after. This proves that it was obstructed mechanically. There is no alternative explanation for the sudden increase in the flow immediately afterwards. But the obstruction did not prevent hyperemia. The blood must have been flowing in spurts its progress being obstructed during contraction and free through widely dilated vessels during relaxation. Fig 5 8 shows further evidence to the same effect. The exercise was interrupted eight

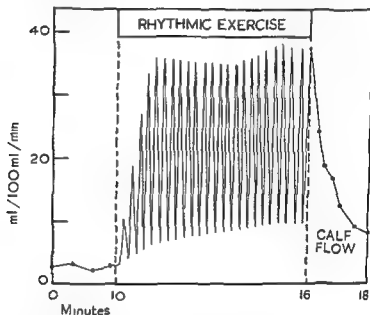


Fig 5 8 Diagrammatic representation of change in blood flow in the calf during strong rhythmic contraction

times for a few seconds each time four times to record blood flows during sustained pressure on the pedal and four times while the subject relaxed the calf muscles as completely as possible. The results show as would be expected, restricted flow during sustained contraction (circles) and free flow during relaxation (crosses). This is seen diagrammatically in Fig 5 9

It is interesting to compare the results obtained in our experiments (Fig 5 8) with those obtained on the dog's gastrocnemius by Kramer Obal and Quensel (1937) and shown in

Fig 5 10 They are very alike Their interpretation too is the same as ours

The experiments just described show that the circulation in calf muscles during strong rhythmic contraction is affected by three factors local vasodilatation mechanical obstruction and the muscle pump They enable us to visualise the spurting blood flow the overall hyperaemia the forceable return of blood to the heart the shrunken veins and paradoxically the redistribution of blood from the calf to other parts of the vascular system

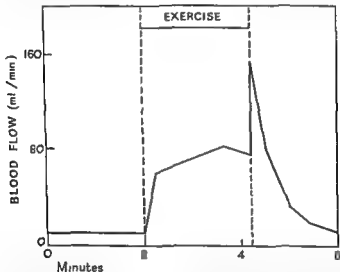


Fig 5 10 Experiment showing the effect of rhythmic exercise on the blood flow through the chloralosed dog's gastrocnemius muscle. The changes are strikingly like those recorded in man Fig 5 8 (Kramm, Obal and Quenel 1937)

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## CHAPTER 6

### THE ACTION OF SYMPATHETIC NERVES ON THE CIRCULATION IN SKELETAL MUSCLE DURING EXERCISE

In Chapter 1 it was shown that the vasomotor centre maintains vasoconstrictor tone in the blood vessels of skeletal muscle. It was natural to wonder whether this was released in exercise and if so to what extent it was responsible for the

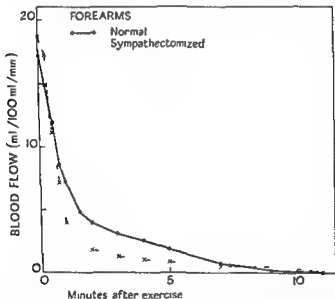


Fig 61 Results showing vasodilatation in sympathectomized muscle after exercise. Average results of experiment on one subject (Crant 1939)

increase in blood flow through the active muscles. It will be remembered that Crant (1938) had found that during exercise the vasodilatation in normal and sympathectomized limbs was similar and concluded that it was due in the main to the action of metabolites. This may be seen in Fig 61 which has been drawn from his results. However athletes find that they run

better if they warm up before exercise and the explanation of warming up might be that the rise in body temperature caused the vasomotor centre to release the constrictor tone in their muscle and so potentiated the vasodilator action of the metabolites.

This possibility was investigated by Barcroft & Dornhorst

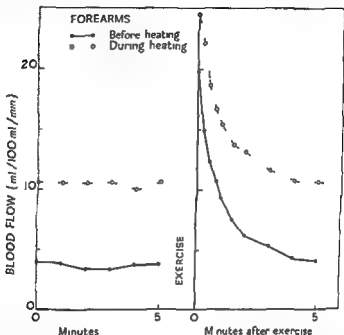


Fig 6. Results showing the effect of releasing sympathetic vasoconstrictor tone in muscle on the resting and post exercise blood flow in the forearm.

Apart from an increase in the general level of blood flow the post exercise changes look alike. To enable more accurate comparison they have been superimposed and graphed in Fig 6.3.

Each subject did 3 rhythmic exercises lasting 3 to 4 minutes before and after release of vasoconstrictor tone. Tone released by immersion of feet in water at 45°C. Plethysmograph water filled temperature 34-35°C.

Average result on 4 subjects

McClatchey and Turner (1951). The general plan of their experiments was as follows. If release of constrictor tone speeded up the circulation in working muscles the rate of accumulation of metabolites should be retarded. At the end of the exercise the hyperemia and blood debt should be reduced (Lewis and Grant 1925, Freeman 1935, Kunkel

Stead and Weiss 1939, Abramson, Katzenstein and Ferris 1941, Eichner and Wilkins 1941). To see if this was so, carefully standardized rhythmic exercises were performed with the forearm or calf and the resulting hyperaemia and its subsidence were measured with the plethysmograph. One or more of the subject's limbs was then immersed in water at 45°C to raise his body temperature and release his constrictor tone (Barcroft, Dornar and Edholm 1947). The exercises were then

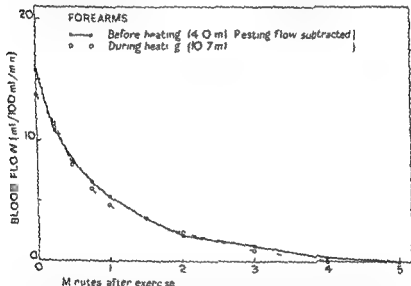


Fig. 63. Post exercise blood flow changes recorded in the forearm muscles before and during release of sympathetic vasoconstrictor tone. Fig. 62 Graphed after subtraction of the respective post exercise resting rates.

The difference in the blood flows (areas under the curves) is only 9.7 per cent (Barcroft, Dornar, de McClatchy and Tanner 1951).

reported and the ensuing vascular changes recorded and compared with those previously obtained.

Fig. 62 shows the results. The resting blood flow was 40 ml per 100 ml forearm per minute. After the release of tone it rose to 10.7 ml. Apart from the increase in the general level of the circulation the post exercise changes looked rather alike. To compare them more accurately the respective resting rate was subtracted from the post exercise rate in each case and they were graphed as shown in Fig. 63. The difference

in the blood debts ( areas under the curves ) was only 9.7 per cent. Further experiments on the calf were done on a much larger number of subjects. Fig. 6.4 shows the results of the first series superimposed after subtraction of the respective resting rates. There was no difference. Fig. 6.5

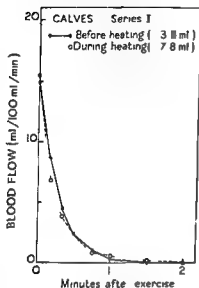


Fig. 6.4

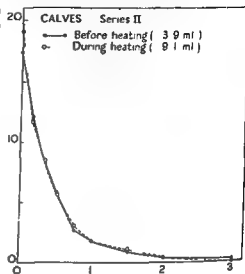


Fig. 6.5

Figs. 6.4-6.5. Post exercise calf blood flows recorded before and during release of sympathetic vasoconstrictor tone in the calf muscle. Graphed after subtraction of the respective post exercise resting rates.

Releasing vasoconstrictor tone scarcely affected the circulatory changes after exercise.

Fig. 6.4. Averaged results of experiments on 14 subjects. Each had 4 and 8 min. rhythmic exercise before and during reflex vasodilatation.

Fig. 6.5. Averaged results of experiments on 9 subjects. Each had 4 and 8 min. rhythmic exercise before and during reflex vasodilatation. (Barcroft, Dornhorst, McClintock and Tanner, 1952.)

shows the results of a second series: the post exercise changes were the same.

Considering all these results on the forearm and calf there was no reasonable escape from the conclusion that the activity of the vasomotor centre had had no effect on the circulatory changes taking place during or after muscular activity. Indeed it could hardly have been acting on the same vessels as the metabolites. If so surely there would have been some

inverse relation between the general level of the blood flow and the blood debt.

To sum up then release of sympathetic vasoconstrictor tone increases the blood flow through muscle (Chapter 1) but apparently not through the same vessels as subserves its metabolic requirements. What is the anatomical basis of this? The facts would be simply explained if the vascular bed contained arterio-venous anastomoses if the vasomotor centre regulated them in the general interests of the circulation and if the capillary bed was controlled by metabolites according to local requirements. But the classical descriptions of muscle vessels by Spalteholz (1885) and Krogh (1922) do not include A-V anastomoses. Yet recent observations on living tissues by Zweifach (1949) have convinced him that minute anastomoses or preferential channels exist in many tissues including skeletal muscles where their presence was hitherto unsuspected. It is very important to see if this can be confirmed. If so our understanding of the circulation in muscle would be considerably extended.

It will be recalled that intravenous infusions of adrenaline caused a sustained increase in the blood flow in muscle due to the action of an unknown circulating hormone (Chapter 3). Experiments were therefore done to see if the release of vasoconstrictor tone by adrenaline would

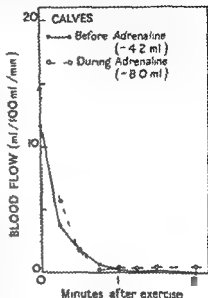


Fig. 66 Results showing that increasing resting muscle blood flow by intravenous infusion of adrenaline scarcely affected the circulatory changes on the calf blood flow during exercise. Each subject did 1 or 2 rhythmic exercises lasting 1 min before and during the infusion. Averages of 6 subjects.

increase the rate of repayment of the blood debt (Swain and Swain 1941). During the exercises the blood flow was probably relatively small as the muscles were never relaxed completely. Fig. 6B shows the results. Adrenaline increased the average resting blood flow in the calf from 4.2 to 8.0 ml per 100 ml per minute. The average post exercise blood flows obtained after subtracting the respective resting rates were again similar. Although the similarity is not quite so perfect as that obtained by Barcroft et al. it is clear that the difference in post exercise repayment is slight. It is worth mentioning that the adrenaline made the exercise more difficult: fatigue did not occur to any greater extent but muscular tremor and incoordination of fine movements impeded the rhythm of action. It appears then that increasing the rate of the circulation in the muscle by adrenaline does not hasten the repayment of the blood debt and this too suggests that the vessels controlled by the sympathetic may be different from those controlled by the metabolites.

The existence of two circulations in muscle—nutritive and anastomotic—may explain an important discrepancy between the results of plethysmographic and sodium clearance experiments. The radio active sodium method introduced by Kety (1949) is briefly as follows. Sodium 24 is injected into a muscle and is cleared from it at a rate depending on the ability of the local circulation to remove it. To determine the clearance counts are made over the muscle with a Geiger Muller counter and plotted semi logarithmically against time. A downward sloping line results whose steepness depends upon the rate of the nutritive blood flow and is denoted by a constant  $k$ . Using this method to study circulation in the gastrocnemius McGirr (1952a, b) found that the rate of clearance from the muscle was decreased during reflex heating. Rapaport, Saul Hyman and Morton (1952) observed that the clearance from the calf muscles was not increased by lumbar sympathetic block. These differences from the results of the plethysmographic method (Chapter I) would be explained if the vessels controlled by the sympathetic in muscle were arteriovenous anastomoses. Increase in blood flow through anastomotic vessels due to reflex heating or lumbar block would not be detected by the sodium clearance method. However the

difference between the results of the two methods may well be due to some other cause and further work is needed to explain it

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## CHAPTER 7

### SYMPATHETIC DENERVATION

Changes in the behaviour of sympathectomized blood vessels can conveniently be divided into two categories—early and late. The early changes have to do with the development of intrinsic tone and the later ones concern the re-establishment of connection with the vasomotor centre. It will be convenient to describe these separately.

#### THE EARLY CHANGES

Goltz and Freusberg (1874) seem to have been the first to notice that the vasodilatation following denervation only lasts a short time. They found that a freshly denervated dog's leg was warmer than its fellow but that the difference did not persist. Other observers have confirmed the phenomenon in animals (McDowall 1938).

In man the early results appeared to conflict. Adson and Brown (1920) found that lumbar sympathectomy caused a permanent rise in the temperature of the toes of  $12^{\circ}\text{C}$ . On the other hand Lewis and Landis (1929) deduced from inspection of the skin that the capillary vessels recovered their tone two days after operation and from palpation of the digital arteries that the arteries had contracted considerably by the fourth day. More recently a number of observers have shown with the plethysmograph that there is very little difference in the blood flow before and some weeks or months after sympathectomy (Grayson 1948; Grant and Pearson 1938; Wilkins and Eichna 1941).

To obtain more quantitative data on the circulatory changes in human vessels following sympathectomy the blood flow in the hand and foot was measured daily with the plethysmograph before and for some time after nerve section. For use in the wards the technique was simplified. Air filled perspex plethysmographs were used and the recording apparatus was mounted on a trolley cupboard. Fig 7.1 shows the apparatus being used to determine the blood flow in the foot. Further

details of the method will be found in the original articles (Barcroft and Walker 1949 Lynn and Barcroft 1950 Walker Lynn and Barcroft 1950) Only the results obtained on limbs operated upon for excessive sweating or deep venous thrombosis will be described here as they alone represent the response of normal human arterial vessels to sympathetic denervation In the case of all of the feet and some of the hands the pre-ganglionic fibres were severed in the case of the other hands

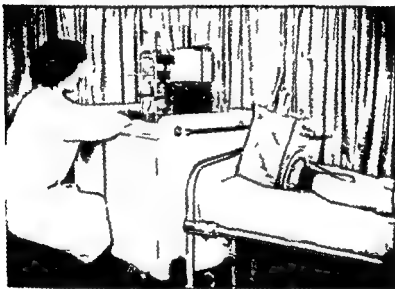


Fig 71 Simple plethysmographic apparatus for use in the ward (Photographed by E V Willmott Postgraduate Medical School of London University)

the section was predominantly though not entirely through the postganglionic fibres

Table IV and Fig 72 (left) show the effect of sympathectomy on the circulation in the hands After disconnection of the vessels from the vasomotor centre and the release of vasoconstrictor tone there was an immediate eight fold increase in the blood flow This hyperaemia subsided quickly on the sixth day the blood flow was only double the initial rate and on the fourteenth the difference was still less The figure shows that the fingers remained warm though unfortunately the temperature records are incomplete

TABLE IV

Blod flow (ml per 100 ml hand or foot)

Sex	Age	Rt or Lt	If re- flection		Op	After op at on					B f operation		After op rat on				
			1 day	1 day		1 day	2 days	3 days	4 days	5 days	6 days	14 day	13 m	2 days	1 day	6 7 days	14 days
HANDS																	
F	35	Rt	34	0	184	380	107	11	67	92	68	59			340	3	3
		Lt	5	6	15	7	106	109	8	76	68	48			350	3	3
M	39	Rt	0	07	456	534	34	162	300	197	180	08			347	29.5	34.3
		Lt	43	89	599	483	77	9	19	04	07	11.8			36	34	33
M	46	Lt	3	09	546	305	99	9	84	21	181	11.5					
		Average	67	52	391	386	227	167	185	144	137	81			343	317	330
Feet																	
F	19	Rt	1	10	180	10	00	10	70	68	76		56	45	304	390	330
		Lt	0	15	150	160	14	110	70	78	90		55	60	300	393	317
F	13	Rt	13	3		183	08	166	92	129	90		66	35	333	310	31.5
		Lt	4			141	1	150	94	134	80		60	30	30	31.5	30
F	40	Lt	40	40		128	145	0	160	130	130		8		295	350	335
		Lt	16	17		80	0	145	146	106	44		19	20	3	354	337
Ave	21	Lt	21	21	165	184	200	149	105	106	85		49	242	250	327	323

A test was re-n-t-d o these d th figures used w those lt need w than o o two d y

A test was not done on these 4th figures used in those 11 feet within a two day

The results obtained on the feet are also shown in Table IV and in Fig 7 2 In general they resemble those obtained on the hands The maximum flow did not occur till two days after the sympathectomy and was only about half that in the hands The final flow 2-3 months later was about double the preoperative one A large number of toe temperatures were obtained the toes were much warmer after division of their sympathetic nerves and they remained so for 2-3 months

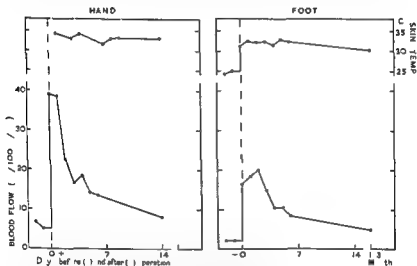


Fig 7 - Results showing the effect of sympathectomy on the blood flow in the hand and foot and on the temperature of the digital skin

The blood flow subsided. The digits remained warm.

Averaged result from Table I (Walker, Lynn and Barcroft 1950)

A number of points need comment. It was surprising that the blood flow did not always rise to a maximum at once. In three of the five hands the maximum was not reached till the day after the operation. Unfortunately the blood flows in four of the feet were not recorded on the day of the operation but in the other two the maximums were recorded on the day after operation in one case and on the second day after in the other. This cannot at present be explained.

The finding that the maximum blood flow in the hand was about double that in the foot (Fig 7 2) which accords with the observations of Greenfield et al (1951) using a different method

is probably because the circulation in these parts is mainly through the skin and the hand contains a relatively much larger proportion of skin

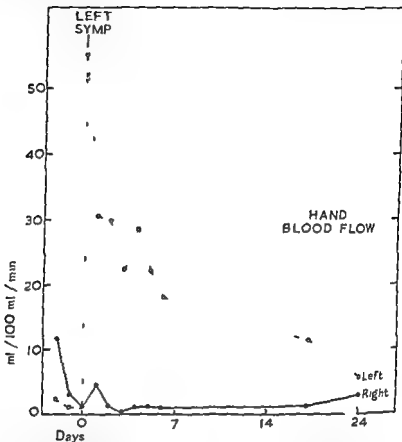


Fig 7.3 Results showing the effect of unilateral sympathectomy on the circulation in the hands

Marked hyperaemia in the ipsilateral hand. No change in the circulation in the contralateral hand

The vasodilatation in the ipsilateral hand cannot be due to any factor connected with the operation other than section of the sympathetic fibre (Walker Lynn and Barcroft 1950)

In several cases of which Fig 7.3 is one example the sympathetic was cut on one side only and the increase occurred on that side alone. This served as a useful control showing that the hyperaemia was not due to release of metabolites from

the traumatized tissue or any other factor connected with the operation other than the sympathetic denervation

In the case of two of the subjects operated upon for the hands preganglionic section was performed on one side and postganglionic on the other (ganglionectomy) as Fig 7 4 shows the results did not appear to differ Fig 7 5 shows that

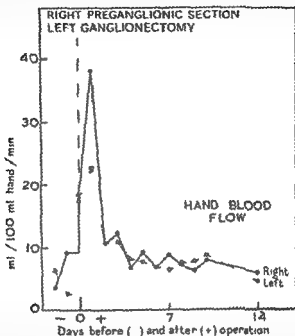


Fig 7 4 Changes in blood flow in the hands after sympathectomy by preganglionic section on one side and by ganglionectomy on the other. The whereabouts of the sympathectomy made no difference to the circulatory changes (Walker-Lynn and Barcroft 1950)

in muscle vessels too the rate of recovery of tone after preganglionic section appears to be much the same as that after ganglionectomy (Duff 1951)

Adson and Brown (1929) found that after sympathetic denervation the toes were warm for many days this was confirmed by our results (Fig 7 2). The fact that they remained warm in spite of the subsidence of the hyperaemia in the foot as a whole cannot at present be explained. The finger tips are known to contain great numbers of A-V anastomoses and

it may be that these regain relatively less tone than the vessels generally in the foot. Another possibility is that of a greater heat loss from each millilitre of blood passing through the toes owing to the increased capacity of the veins after sympathetic

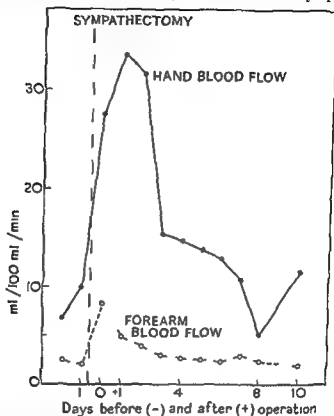


Fig 7.5 Records of the effect of sympathectomy on the blood flow in the forearm and hand

The maximum flow was recorded earlier in the forearm; it was smaller and it subsided more quickly.

This may have been due to slight differences in the behaviour of the blood vessel in muscle and skin. (Duff 1951)

denervation (Goetz 1950). Or it may be that the digits remain warm because they cannot sweat.

The vascular response first described in the hand and foot probably represents essentially the effect of sympathectomy on the cutaneous vessels. The response of the vessels in the forearm probably that of skeletal muscle blood vessels has been

examined with the plethysmograph by Duff (1931). The results obtained on four arms with normal blood vessels are shown in Fig. 75 and the figure also shows the results obtained simultaneously in the hands of the same subjects. The general resemblance is clear. Duff described the following differences. The maximum was reached sooner in the forearm than in the hand; its extent was smaller and the regain of intrinsic tone was quicker. The maximum was of the same order as that recorded after blocking the deep nerves to the forearm muscles (Chapter 1). Similar results were obtained in the calf by Dornhorst (1951) who found that the maximum calf blood flow occurred on the day of the operation.

We must now turn to the explanation of the return of tone. It is generally recognized that after section of a nerve the distal part undergoes an ordered process of destruction known as Wallerian degeneration. These changes take place at much the same rate in all mammals (Young 1950). Cannon and Rosenbleuth (1949) have shown that the consequences of denervation extend beyond the distal neurones to the effector cells. They do not die but they undergo very fundamental alterations in their way of life. The striated the smooth the cardiac muscle cell and the gland cell are all affected. The chief manifestation of this is their increased sensitivity to chemical stimulation. It holds for excitation as well as for inhibition and it applies to stimulation by the chemical transmitters adrenaline and acetylcholine which act outside the cell and to stimulation by other drugs which only act after penetration. Supersensitivity occurs to a less extent if the nerve supply is cut through the penultimate neurone.

The facts have been aptly summarized by Cannon and Rosenbleuth (1949) in the law of denervation. It runs

When in a functional chain of neurones one of the elements is severed the ensuing total or partial denervation of some of the subsequent elements in the chain causes a supersensitivity of all the distal elements including those not denervated and effectors if present to the excitatory or inhibitory action of chemical agents and nerve impulses. The supersensitivity is greater for the links which immediately follow the cut neurones and decreases progressively for more distant elements.

The known changes in the denervated cells which cause the



super-sensitivity are very imperfectly understood. They may affect among other things enzymic systems and the permeability of the cell wall to potassium and phosphorus (Lyman 1942, Friedlander, Perlman and Chrukov 1941) and to histamine

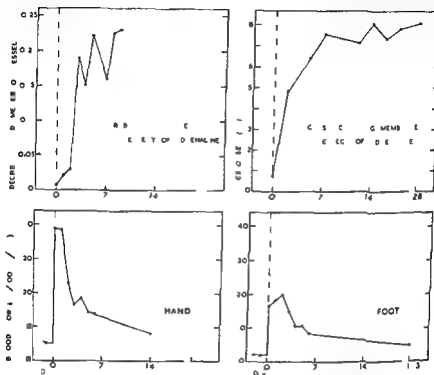


Fig 76 Results showing that the time relations for the development of intrinsic tone in the vessels of the hand and foot after sympathectomy closely resemble those for the development of a lrenaline supersensitivity in the rabbit ear vessels and metatarsal membrane

Intrinsic tone develops at the same time as the phenomena described by Cannon and Rosenbleuth's law of denervation (Taylor and Humpel 1937, Taylor and LeCompte 1941)

(Cannon and Rosenbleuth 1936) The permeability of capillaries may also be affected (Gabbe 1926, Engel 1940)

Many of these facts have been established for many years and have been the basis of attempts to explain how tone is regained. The connection between the law of denervation and the regain of tone appears to us to be still more firmly established by the experiments on the blood flow through the hand

and foot. For in Fig. 76 shows the rate of regain of tone is so remarkably similar to the rate of development of adrenaline supersensitivity. After comparing these curves it is difficult to escape the conclusion that the events they represent must be very closely related. Sympathectomy must start a chain of biophysical and biochemical events in smooth muscle which are manifested by supersensitivity and the regain of tone.

The following hypotheses have been suggested to explain the return of tone

- (1) It may be due to the arteries becoming supersensitive to circulating adrenaline (Freeman, Smithwick and White 1934; Smithwick, Freeman and White 1934; White, Okelberry and Whitelaw 1936; Ascroft 1936)
- (2) It may be due to supersensitivity to an unknown hormone (Grant 1935; LeCompte 1941)
- (3) It may be the direct effect on the contractile process of intrinsic changes in the smooth muscle (Cannon 1937; Doupe 1943)

Those in favour of the adrenaline sensitivity theory have based their view principally upon experiments showing that sympathectomized vessels in man and animals are supersensitive to injected adrenaline and to the secretion of the suprarenal gland when excited by insulin or struggling. That they are indeed supersensitive to adrenaline in some subjects has recently been shown with the plethysmograph by Duff (1932) and may be seen in Fig. 77. However these findings are in themselves no proof that regain of tone is due to supersensitivity to circulating adrenaline since in the resting state there may not be sufficient in the blood to cause the vessels to contract. This question might be settled by ascertaining if vessels that had regained tone could be reopened by an adrenergic blocking agent.

Grant (1935) and LeCompte (1941) showed very clearly how the sympathectomized arteries of the rabbit a ear became supersensitive to an unknown constrictor substance. It was not adrenaline or pituitrin since it was secreted in the adrenalectomized and in the hypophysectomized animal. However there is no conclusive evidence for the presence of an active constrictor substance in the blood of a normal resting human being.

### THE LATE CHANGES

Paterson Ross (1946) has stated that the results of a well planned and correctly executed sympathectomy are permanent. On the other hand Simmons and Sheehan (1939) and Haxton (1947) found that in many cases vasomotor and sudomotor reflexes returned. The question of the completeness and permanence of sympathectomy is obviously important in both clinical and research work. So we shall now describe tests performed on a large number of sympathectomized arms to assess the completeness of the denervation.

Altogether 56 were studied (Barcroft and Hamilton 1948, b). Most of them had been operated upon for vascular disease. In all cases the sympathetic path was cut through the preganglionic fibres (Smithwick's operation 1940). The interval between the operation and the performance of the test varied from 1 month to 6 years.

The completeness of the sympathectomy was first assessed with the plethysmograph which gives rather more quantitative information about the blood flow than the finger temperature method used by the previous authors. The principle of the test is that in normal subjects warming the body causes a central release of vasomotor tone which is manifested by flushing and increased blood flow in the extremities. In sympathectomized ones the circulation in the extremities is not affected (Landis and Gibbon 1933). The test was carried out as follows (Fig 7.8). The blood flow in the hand was recorded at 5 minute intervals for a preliminary control period of half an hour. The subject was then covered with two blankets and both his or her feet immersed to well above the ankles at 45° C. Recording continued for an hour more. Afterwards the blood flow at the end of the period of heating was divided by the initial resting blood flow: the result was the heating ratio. In the experiment shown in Fig 7.8 the heating ratio was 6: warming the body had increased the blood flow in the hand sixfold. In a completely sympathectomized subject the heating ratio would have been approximately 1.

The heating ratios of some normal hands are shown in Fig 7.9. In all of them warming the body caused a three to fivefold increase in the circulation. The figure shows also the

results obtained on the 56 sympathectomized hands. These are arranged from left to right in increasing order of interval of time between operation and testing. All hands tested within six months of operation had heating ratios of about 1—i.e.

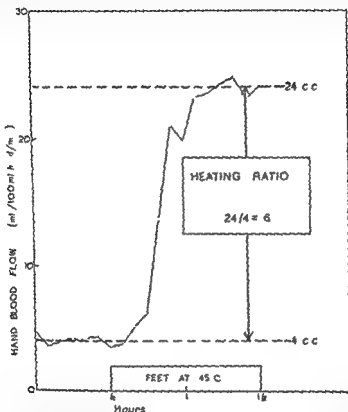


Fig. 8. Vasomotor test for sympathetic vasomotor innervation of the hand.

The hand blood flow is recorded before and during immersion of the feet in warm water to release sympathetic constrictor tone. The increase in flow or heating ratio is a useful index of sympathetic vasomotor activity [Barcroft and Hamilton 1948a].

reflex heating had no significant effect on their vessels. In contrast to these early results many hands tested between one and six years after denervation had heating ratios considerably greater than 1—that is warming the body had elicited reflex vasodilatation.

In many cases the test was repeated and instead of warming the body to release the vasoconstrictor tone the deep nerves were blocked (radial median and ulnar Chapter 1) The results of the two different methods were similar

Fortunately the state of the sympathetic paths could be assessed by another altogether different test a sudomotor test

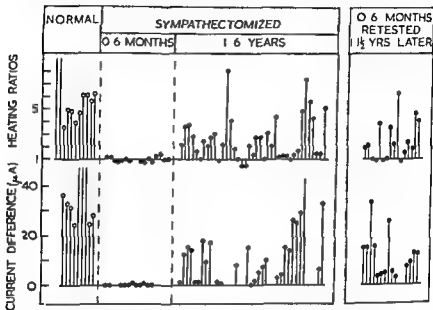


Fig. 8 Results of vasomotor and sudomotor tests performed on 16 limbs after sympathectomy arranged from left to right in order of time interval between operation and testing

Vasomotor and sudomotor reflexes were absent in limbs tested 6 months or less after operation but present in limbs tested 1-6 years after operation

The results show that the sympathetic re-establishes connection with the blood vessels and sweat gland in the hand (Barcroft and Hamilton 1948a, b)

The principle of this test is that the resistance to the passage of a current through the body lies almost entirely in the skin and is determined mainly by the activity of the sweat glands. This in turn depends on nervous excitation mediated by the sympathetic (Richter 1946). The apparatus for testing the resistance of the skin consisted of a 44 volt battery with one of the poles connected to an indifferent electrode and the other through a microammeter to a brass applicator with an insulated

handle (Haxton 1947). The test was carried out as shown in Fig 7.10. The indifferent electrode was strapped in the axilla. The skin current over the pulp spaces of the thumb, middle and little finger was measured at intervals of 5 minutes. After a control period of half an hour the subject was warmed to induce maximal activity of the sweat glands and the ulnar nerve was blocked with 4 per cent procaine and adrenaline to prevent any impulses from reaching the little finger. Skin current readings continued for another hour. After the test the current that had passed through the little finger (control skin) at the end of the period of body warming was subtracted from the average of the currents that had passed through the thumb and middle finger (test skin). The result was the current difference. In the experiment shown in Fig 7.10 owing to the relative moisture of the test skin caused by activity of the sympathetic sudomotor fibres there was a current difference of 24½ microamps. In completely sympathetomized hands the current difference is approximately zero since there is no material difference in the amount of sweat in the test and control skin areas.

The current differences of a number of normal hands are shown in Fig 7.9. In all of them there were quite large current differences. The figure shows also the results obtained on the 56 sympathetomized hands. They are arranged as before in order of increasing interval of time between operation and investigation and vertically below the corresponding results for the vasomotor test. The results of the sudomotor test like those of the vasomotor one fall into two groups—those obtained on them six months after sympathetic denervation and those obtained a year or more after. All hands tested within six months had very small current differences. Many of the others however had quite large ones. Warming the body had caused sweating.

Considering the results of both vasomotor and sudomotor tests it was clear that there was no evidence of any significant connection between the brain and the hand for several months after sympathetomy. However a year or more after operation vasomotor and sudomotor reflexes were often present.

Finally sixteen of the seventeen hands tested within six months of sympathetic denervation were retested 1–1½ years

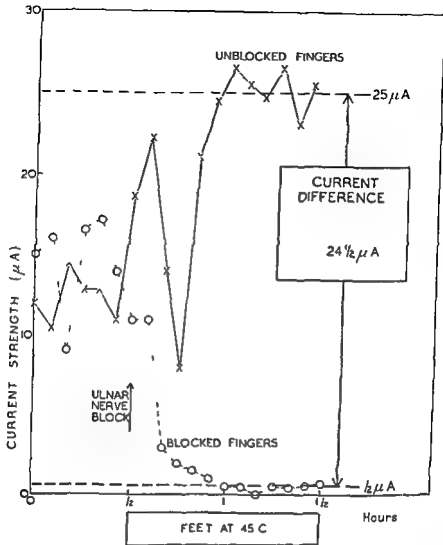


Fig 7 10 Sudomotor test for sympathetic innervation of the hand  
The electrical conductivity is measured through

(1) The skin of the tips of the middle finger and thumb in which maximal activity of the sweat gland has been excited by warming the subject. The results are averaged (test skin)

(2) The skin of the tip of the fifth finger which has been deprived of sympathetic activity by ulnar nerve block (control skin)

The difference between the conductivity of the test and control skins (current difference 1-2) is a useful index of sympathetic sudomotor activity (Barcroft and Hamilton 1949a)

later. The results seen in Fig. 7.9 showed that vasomotor and sudomotor reflexes had returned to many of these hands.

A number of points need further comment. In the first place the blood vessels of all the hands (seventeen) examined within six months of operation must have been to all intents and purposes completely sympathectomized by cutting the rami communicantes of T2 and T3 and the sympathetic chain between T3 and T4 as was done at operation in every case. The existence of other paths that would have been left intact by these sections is suggested by the work of Huntz, Alexander and Furcolo (1938), van Buskirk (1941), Kargis and Huntz (1942), Skoog (1947), Ray and Console (1948) and Boyd and Monro (1949). However as far as the blood vessels of the hands we examined are concerned such paths cannot have been of much importance. We cannot speak with such assurance about the completeness of the sympathetic denervation of the sweat glands. In the first place our apparatus was not very sensitive and in the second we were concerned only with the glands in the skin of the finger tips.

It would be of great interest to know how the new connection established by the sympathetic compares with the original as regards function. No doubt there will be great differences from one individual to another. It is worth examining the meagre data available. The figures in Table V suggest that in most subjects the new connection functions poorly. The table shows that 1-5 years after sympathectomy the hands

TABLE V

	Sympathectomized		Normal
	1-6 months	1-5 years	
Average heating rate	1.0	.8	9.5
Average hand blood flow during body warming (ml. per 100 ml. per minute)	9.1	11.1	25.1
Effect of operation on frequent vasospastic attacks—			
cured		18	
relieved		14	
unaltered		4	



resembled completely sympathectomized ones rather than normal ones both as regards their heating ratios and blood flows during reflex vasodilatation (Hamilton 1947). This suggests a deficient innervation. However it may have been rather better than would appear from the figures for vascular

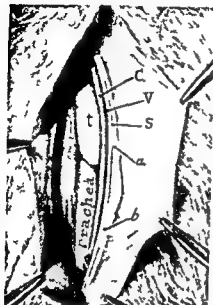


Fig 7.11 Drawing showing how regenerating nerve fibres bridge a gap of  $\frac{1}{8}$  inch in a cat's right cervical sympathetic chain.

The nerve ends  $a$  &  $t$  of the sympathetic nerve  $S$  are slightly thickened and are joined by numerous small thyroid gland  $C$  common carotid artery  $I$  vagus nerve (Lee 1930)

disease would have slightly restricted the capacity of the vessels to dilate. There is another reason for thinking that little function returns. It concerns the beneficial effect of the sympathetic denervation on the vascular disorder. Of 36 limbs sympathectomized for frequent vasospastic attacks and first seen 1-5 years later 18 had had no recurrences since the operation. Yet to many of them the reflexes had returned. This too suggests that the reconnection was a poor one.

How the reconnection in the sympathetic path comes about cannot at present be explained. There are two possibilities. The development of a new path in the rami communicantes above the level of T2 and regeneration of the cut fibres

across a gap of about an inch. The former has been described in the cat by Geohagan and Aidar (1942). Following interruption of preganglionic pathways to the forebrain preganglionic pathways developed higher up from roots which normally contribute nothing to the forebrain. As regards regeneration the powers possessed by the sympathetic in animals at any rate seem to be very much greater than those with which somatic sensory and motor fibres are endowed. An experiment of Lees (1930)

is worth quoting. Lee cut a cat's cervical sympathetic and fixed the ends so that they were separated by an inch of muscle. After 27 days stimulation of the proximal end excited the typical retraction of the mictitating membrane and enlargement of the pupil. Stimulation of the tissue between the nerve ends showed that the regenerated fibres had taken a course partly through the muscle and partly round it. Histological sections confirmed that regeneration had occurred. The results of another of Lee's experiments are shown in Fig. 711.

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## CHAPTER 8

### THE ACTION OF ADRENALINE AND NORADRENALINE ON THE CIRCULATION IN THE SKIN

Both adrenaline and noradrenaline cause pallor of the face in man. This effect is usually attributed to the direct constrictor action of the amines on the cutaneous vessels. However a more detailed study of the problem reveals certain interesting facts in regard to the action of these substances on the vascular system in the skin.

Although visual inspection of the skin colour may indicate its vascular state, objective studies of the skin surface are unsatisfactory if we are attempting to follow rapid changes in skin blood flow. Skin temperature measurements are of little use in such investigations because the change in surface temperature lags behind an alteration in blood flow by an appreciable interval. As an extreme example of this it may be shown that when the blood flow in a limb is completely occluded by a pressure cuff there is only a gradual fall in skin temperature. Also if the blood flow increases from a state of moderate dilatation to one of full dilatation only a small rise of skin temperature occurs, whereas changes from moderate dilatation to a lower flow may be accompanied by a considerable fall in skin temperature (Lewis 1927). Heat elimination (Cooper et al. 1950) is also unsatisfactory as it reflects average changes which have occurred over a period of time. The use of the hand or foot plethysmograph avoids the response lag and gives an accurate picture of the variation in flow. It has the disadvantage however that measurements of blood flow are made on a specialized skin site and on a structure containing some muscle. Nevertheless the blood flow changes in the hand and foot reflect predominantly alterations in the skin vessels (Abramson and Ferris 1940).

We will consider in detail the changes in blood flow in the hand during and after infusions of adrenaline or noradrenaline. Precautions have to be taken lest the response is due to chance

for the hand blood flow undergoes considerable spontaneous variation and is also influenced by emotional stimuli (Wilkins and Eichler 1941)

### THE VASOCONSTRICTOR ACTION OF ADRENALINE AND NORADRENALINE

In order to compare the constrictor properties of these substances on the skin blood vessels infusions were made into the brachial artery thus avoiding any central effects which these substances might cause. Because of the experiences gained in an earlier investigation infusion rates of  $\frac{1}{32}$ ,  $\frac{1}{16}$ ,  $\frac{1}{8}$  and  $\frac{1}{4}$   $\mu\text{g}$  per minute were used. Table VI summarizes the findings. There appears to be little difference in the constrictor activity of the two substances. This is somewhat surprising for the facial pallor caused by adrenaline is always more evident than the pallor resulting from a similar amount of noradrenaline. What is the explanation of this apparent anomaly? We recognize the preponderance of skin over muscle in the tissues of the hand but some muscle is present

TABLE VI

*The hand blood flow response to intra arterial infusions of adrenaline and noradrenaline<sup>1</sup>*

Dose $\mu\text{g}/\text{min}$	Average of 10 subjects Average blood flow (ml/100 ml min)		
	Before	During	After
<i>Adrenaline</i>			
$\frac{1}{32}$	12.9	12.0	13.1
$\frac{1}{16}$	10.3	8	10.9
$\frac{1}{8}$	12.1	6	10.9
$\frac{1}{4}$	9.6	2.9	8.6
<i>Noradrenaline</i>			
$\frac{1}{32}$	9.4	8.0	7.7
$\frac{1}{16}$	10.2	"	10.0
$\frac{1}{8}$	11.1	4.4	9.3
$\frac{1}{4}$	10.2	2.7	7.7

<sup>1</sup> Intra arterial infusions of adrenaline at  $\frac{1}{4}$   $\mu\text{g}/\text{min}$  did not cause any vasoconstriction in the hand of Duff's experiments (Fig. 7.7). In this respect they differ from those seen in Table VI. This discrepancy is probably due to small differences in the vascular responses of the subjects and in the procedures and analytical methods. It is unlikely that the conclusions of either investigator are incorrect.

(Abramson and Ferris 1940). Therefore the blood flow through the hand is the sum of both skin and muscle blood flow. Now in small doses as used in this study adrenaline causes a transient dilatation in muscle blood vessels followed by a return to the resting value whereas noradrenaline causes a powerful vasoconstriction (Chapters 3 and 4). Therefore doses of adrenaline which reduce the blood flow to say 25 per cent of its resting value accomplish this almost entirely by a skin vasoconstriction while noradrenaline reduces the muscle blood flow in addition to decreasing the skin flow. Therefore one can conclude that adrenaline is stronger in constrictor action on skin vessels than noradrenaline which is in keeping with the impression gained from visual inspection.

#### THE CENTRAL DILATOR ACTION OF ADRENALINE

After intravenous infusions of moderate amounts of adrenaline in man flushing of the skin of the face frequently occurs. This had been attributed to reactive hyperaemia following the vasoconstriction caused by the action of adrenaline on the blood vessels. It appeared to have its counterpart in the vessels of the hand for in a small series of subjects it was clear that the hand blood flow increased after the intravenous infusion was discontinued. The after dilatation was not seen in *sympathectomized limbs* nor after *intra-brachial infusions* in normal ones (Swan 1950). As this seemed to be of some importance the matter was more carefully examined (Swan 1951).

The effect of intravenous infusions of adrenaline and noradrenaline on the hand blood flow was studied using a plethysmograph filled with water at 33°C. The room temperature was maintained at 21°C. Under these conditions subjects chosen at random from a class of medical students showed a surprisingly consistent response to 20 µg adrenaline per minute and to 20 µg noradrenaline per minute. Intravenous infusions of either of these substances for 3 minutes caused a decline in blood flow for approximately the duration of the infusion. In the case of noradrenaline the blood flow returns to about the previous level after the infusion is discontinued. With adrenaline however the phase of constriction is succeeded by an increase in blood flow which occurs with sufficient frequency

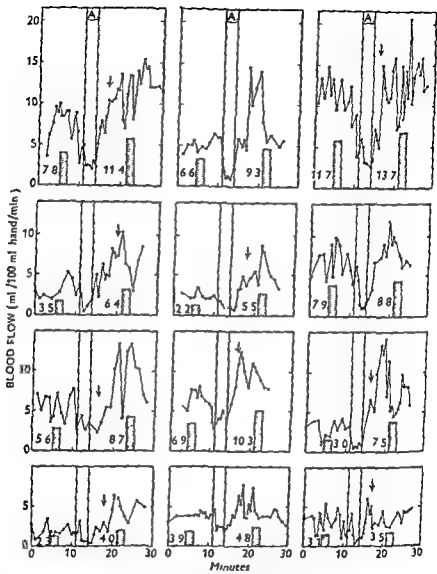


Fig 8.1 Result showing hyperaemia in the hand and flushing of the face following intravenous infusions of adrenaline

The shaded blocks represent (half scale) the average flow recorded in the periods 0-10 and 17-27 min. 3 min infusions at  $20 \mu\text{g/min}$ . The arrows denote the beginning of flushing (Swan 1961)

not to be due to chance. Twelve successive experiments in which infusions of 20  $\mu$ g adrenaline were given to normal medical students are depicted in Fig 8.1. Table VII gives a summary of the findings in a number of these experiments.

It must be pointed out that in the experiments mentioned above the adrenaline and noradrenaline affected the tissues besides the vessels in the hand and alterations in cardiac output, blood pressure and heart rate occurred. It was therefore decided to carry out a similar series of experiments using the technique of brachial artery infusion and by giving a dose sufficient to cause a powerful constriction. By this method a study of the direct effect of adrenaline and noradrenaline on the vessels of the hand could be made while the central effects were avoided. Smaller amounts of adrenaline were used for the drug was not diluted in the general circulation as during intravenous infusions. The findings are shown in Fig 8.2. During the period of infusion the hand flow is much reduced. No after dilatation was observed in these experiments or in the experiments described in the first section of this chapter in which smaller doses were infused intra-arterially.

TABLE VII

*The hand blood flow response to infusions*

(Each group is the average of the ten most recent experiments)

		Average blood flow (ml / 100 ml hand / min)			Significance of any increase after the infusion
		Before	During	After	
<b>Normal subjects</b>					
<b>1. Intravenous</b>					
Adrenaline	10 $\mu$ g	8.4	4.4	8.8	P = .5
	20 $\mu$ g	7.8	2.8	9.8	P < .001
Noradrenaline	10 $\mu$ g	8.1	3.8	9.1	P = .2
	20 $\mu$ g	8.0	3.1	7.8	
<b>2. Intra arterial</b>					
adrenaline	$\frac{1}{2}$ $\mu$ g	7.1	1.0	4	P = .5
<b>Sympathectomized</b>					
Intravenous	10 $\mu$ g	7.6	2.6	7.1	— 4 subjects
Adrenaline	20 $\mu$ g	6.6	1.8	5.9	— 11 subjects

Room temperature 21°C Plethysmograph water temperature 33°C 3 minute infusions



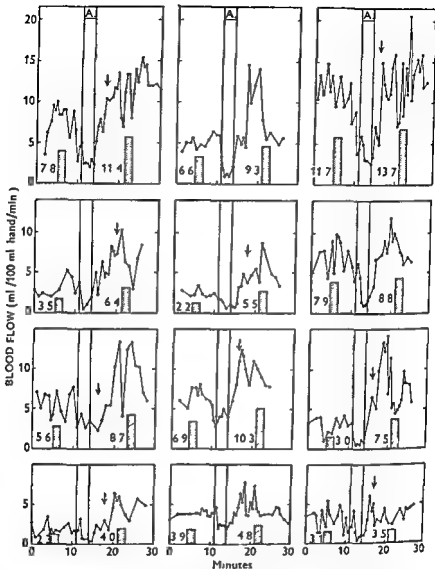


Fig 81 Results showing hyperaemia in the hand and flushing of the face following intravenous infusions of adrenaline

The shaded blocks represent (half scale) the average flows recorded in the periods 0-10 and 17-27 min. 3 min infusions at  $0 \mu\text{g/min}$ . The arrows denote the beginning of flushing (Swan 1951)

While the noradrenaline flush is of rather a dusky tint the adrenaline flush is bright and intense and is accompanied by a sensation of warmth which spreads over the body—but is chiefly experienced in the face and hands

It is clear that the flushing has its counterpart in the hand blood flow response. As we have pointed out there is a significant increase in blood flow in the hand following intravenous infusions of 20  $\mu$ g adrenaline per minute for 1 min. The changes following noradrenaline and smaller doses of adrenaline are not significant. What is the cause of this increased blood flow? A change in blood flow may result from an alteration in the arterial pressure into the organ or from a change in the vascular resistance in the blood vessels themselves. Increase in arterial pressure could not account for the increase in blood flow after adrenaline since blood pressure observations make it clear that there is no increase. Moreover the observations of Green et al show that flushing of the face coincides with a phase of hypotension. Therefore it is reasonable to consider that there is in fact a dilatation of the blood vessels after the termination of the adrenaline infusion. This dilatation might result from the direct action of substances on the blood vessels or it might be due to changes in the nervous influences which regulate the vessels. The first of these alternatives seemed likely on the grounds that the skin vessels had been constricted for the duration of the infusion and dilator metabolites might have accumulated locally. But this possibility cannot be the explanation for as we have pointed out earlier intra arterial infusions are not followed by dilatation. It might be argued that in the intravenous experiments the adrenaline liberated a dilator substance from some central organ into the general circulation and that this substance was then borne by the blood to the skin where it caused dilatation. To test this hypothesis the response to intravenous adrenaline was studied in sympathectomized subjects. Fig 8.3 shows that no dilatation followed the infusion. By elimination we may conclude that the dilatation which follows intravenous adrenaline in normal subjects is due to alteration in the nervous control of the blood vessels. We may be more precise for Arnott and Macle (1948) have shown that the skin of the little finger does not contain dilator nerve fibres.

It is probable that the whole hand is similar. Therefore the adrenaline dilatation is due in fact to an inhibition of sympathetic constrictor nerve impulses. How may this inhibition of constrictor tone come about? It is unlikely to be due to a depressor reflex because it frequently coincides with a phase of hypotension. But there is considerable evidence to show that adrenaline affects autonomic transmission. This has been shown in animals following the injection of very small doses of

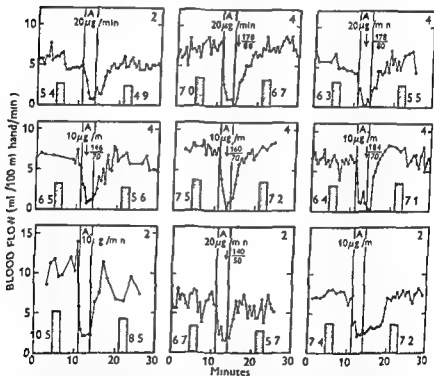


Fig. 83 Results showing that intravenous adrenaline infusions in sympathectomized subjects are not followed by hyperaemia in the hand.

The hyperaemia after intravenous infusions in normally innervated hand (Fig. 81) cannot be due to the liberation of a vasodilator substance into the general circulation and its subsequent action on the hand vessels.

It is probably due to a central dilator action of arenaline mediated by the sympathetic and abolished by sympathectomy.

The shaded blocks represent (half scale) the average flow recorded in the period 0-10 and 17-27 min. 3 min intravenous infusions. The arrow indicated the time at which the maximal blood pressure given on the diagram was recorded. The number of limbs sympathectomized in doing the test limb is shown in the top right hand corner. (Swan 191)

adrenaline and after reflex stimulation of the sympathetic supply to the adrenal gland (Marrazzi 1939a, Bulbring and Burn 1942, Posternak and Larabee 1950). We may conclude that the after dilatation seen in normal limbs is due to direct depression of vasoconstrictor tone probably in the sympathetic ganglia.

Finally—what is the significance of this mechanism? We may consider it either as part of the emergency reaction (Cannon 1929) or as a protective mechanism (Marrazzi 1939b) or as a harmful mechanism (Bulbring and Burn 1942). As regards the third we feel that it is unlikely that under normal conditions sufficient amounts of adrenaline are liberated to cause a harmful hypotensive state; also we consider that adrenaline shock depends on an inability of the blood vessels to respond to pressor hormones and this should not result from ganglionic blockade or depression of nervous vasoconstrictor tone. The inhibition of vasomotor tone may on the other hand do much to mitigate against excessive rises of blood pressure thus acting as a protection against harmful effects.

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## CHAPTER 9

### THE ACTION OF ADRENALINE AND NORADRENALINE ON THE GENERAL CIRCULATION

The presence of both adrenaline and noradrenaline in the human body makes it of great interest to compare their actions on the general circulation. The more so since they differ remarkably.

The effects of intravenous infusions have been studied by Goldenberg, Pines, Baldwin, Greene and Roh (1948) and by Barcroft and Starr (1951). Small differences in the findings may be explained by the fact that the rates and durations of the infusions differed in the two investigations. Both authors recorded the changes in arterial blood pressure and cardiac output. Goldenberg et al. used the cardiac catheterization technique. Barcroft and Starr the ballistocardiograph.

The effects of infusions at the rate of  $10 \mu\text{g}$  per minute may be summarized as follows. First as regards symptoms and signs. With adrenaline an early sensation was a curious feeling of expectancy with a transient mild tingling all over the body. Then there followed an increase in depth and rate of respiration and the subjective symptoms associated with hyperventilation. It was possible to hold a moderate inspiration for only about 10-15 sec. About 10 sec. after the start of respiratory symptoms the heart rate increased—but this increase might not be noticed by the subject for several seconds. Gradually the force of beat increased for a further  $\frac{1}{2}$  min. after which the rate frequently fell back to a few beats above its resting value. The subject remained aware of the forcefulness of the heart beat. Shortly after the start of cardiac symptoms a feeling of fatigue spread into the back—and into both legs. A coarse tremor of the extremities was common. After the first two minutes the symptoms diminished very considerably.

With noradrenaline the symptoms were very different. The feeling of anxiety or expectancy was absent in most subjects although two subjects reported apprehension with noradrena-

line and no psychical symptoms with adrenaline. Respiration was increased but there was no palpitation fatigue or muscle tremor. Infusion of both amines caused a facial pallor but adrenaline to a greater extent than noradrenaline.

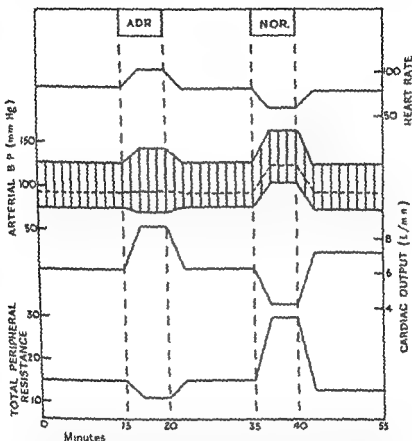


Fig. 91. Diagrammatic representation of the effects of intravenous infusions of adrenaline and of noradrenaline on the heart rate, arterial blood pressure, cardiac output and total peripheral resistance.

(The initial transient decrease in the arterial blood pressure which occurs during infusions of adrenaline (Fig. 93) is not shown.)

Other changes are shown diagrammatically in Fig. 91. Adrenaline caused tachycardia which like the palpitations usually subsided though in this case not altogether during the course of the infusion (see also Hume 1927). Noradrenaline

on the other hand caused bradycardia. Before this curious paradox can be discussed the other circulatory changes in Fig 91 must be described. Adrenaline did not have much effect on the mean blood pressure it raised the systolic but it either did not affect or lowered the diastolic. Noradrenaline had much greater effect because it raised both the systolic and diastolic pressures (see also Barnett et al, 1950). Adrenaline increased the cardiac output whereas noradrenaline either did not affect it (Goldenberg et al) or decreased it (Barcroft and Starr). The changes in the total peripheral resistance were calculated from the cardiac outputs and mean blood pressures. Adrenaline decreased the overall resistance whereas noradrenaline increased it. That is adrenaline acted as an overall vasodilator, noradrenaline as an overall vasoconstrictor.

To return to the explanation of the different effects of the two substances on the heart rate. Both excite the isolated and atropinized hearts (West 1947, Ahlquist 1948) adrenaline more so than noradrenaline. But in the human subject this action will be opposed by increased vagal inhibitory tone reflexly excited by the rise in the mean blood pressure. This rise is less with adrenaline than with noradrenaline. The difference in their actions on the heart rate in man is therefore probably due to the predomination of local excitation with adrenaline and of reflex inhibition with noradrenaline.

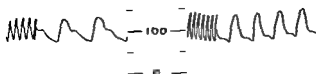
The different actions of the two substances on the diastolic pressure is probably due to their different effects on the peripheral resistance. During infusions of adrenaline in spite of the tachycardia and increased output the blood probably passes so rapidly through the peripheral resistance that there is time for the pressure to fall precipitately between two successive heart beats. With noradrenaline however although there is bradycardia and perhaps decreased output the escape of the blood from the constricted arteries is slow and the change in pressure during diastole is comparatively small.

Studies of the arterial pulse contour changes are in accord with these observations. Using a low displacement capacitance manometer Peterson, Duff and Swan (1950) recorded the changes in pulse contour during infusions of adrenaline or noradrenaline. Fig 92 is typical of their findings.

In the case of adrenaline it is clear that the increased pulse

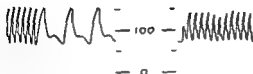
# ADRENALINE

10  $\mu\text{g}/\text{min}$



Before

1 1/2 min after start

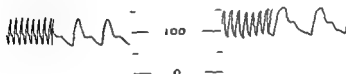


Just before end  
of 10 min infusion

17 min after  
end of infusion

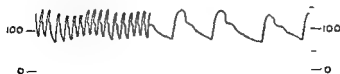
# NORADRENALINE

10  $\mu\text{g}/\text{min}$



Before

2 min after start



10 min after start

Fig 9 - Tracings of the arterial blood pressure recorded with a Lilly intra-arterial capacitance manometer during intra-venous infusions of adrenaline and noradrenaline

**Adrenaline** - the increased pulse pressure and pulse rate signify increase in stroke and minute volume - the absence of a corresponding rise in the mean blood pressure signifies peripheral vasoconstriction

**Noradrenaline** - the decreased pulse pressure and rate signify decrease in stroke and minute volume - the rise of mean blood pressure signifies peripheral vasoconstriction



pressure and pulse rate signify increased stroke volume and increased cardiac output and the absence of a corresponding rise in the mean blood pressure signifies peripheral vasodilatation. In the case of noradrenaline the decreased pulse pressure and pulse rate signify decreased stroke output and minute volume, and the rise of the mean blood pressure signifies peripheral vasoconstriction.

To turn now to the whereabouts in the peripheral vascular system of the vasodilatation caused by adrenaline. In what parts of the body is its action so different from that of the other substance? Evidently not in the skin where both cause pallor. Fortunately in man the circulations through most of the internal organs can be studied individually and the results show that the blood flow through the liver, kidneys, skeletal muscles and brain accounts for most of the output.

Bearn, Billing and Sherlock (1951) have described the effects of the two hormones on the liver blood flow. They used the bromsulphalein (BSP) dye method. The principle is as follows. The dye is infused intravenously at a known rate, the liver abstracts it from the blood at the same rate and excretes it in the bile. The liver flow is calculated on the Fick principle from the rate of hepatic uptake (infusion rate) and the difference in the amounts of dye in the blood entering and leaving the liver (estimated in samples taken by arterial puncture and by hepatic venous catheterization) (Bradley, Ingelfinger, Bradley and Curry, 1945). Bearn et al. found that adrenaline increased the liver blood flow by about 100 per cent, noradrenaline did not materially alter the liver blood flow.

The circulatory changes in the kidneys have also been studied. Barclay, Cooke and Kenney (1947) measured the renal plasma flow in eight subjects before and during 25–40 minutes intravenous infusion of adrenaline at rates of infusion varying from 0.5 to 10  $\mu\text{g}$  per minute. Constriction occurred in every subject, the average decrease in flow being 40 per cent. They were not concerned with the effect of noradrenaline which was examined later by Barnett, Blacket, Dipoorter, Sanderson and Wilson (1950). It too caused constriction but apparently not so much as adrenaline, since even with more than double the rate of infusion (20–30  $\mu\text{g}$  per minute) the average decrease in flow in six subjects was only 20 per cent.

The blood flow through the skeletal muscles probably accounts for another large fraction of the cardiac output at rest. It will be remembered that after the transient vasodilatation in the forearm had passed off the blood flow remained approximately doubled (Allen et al 1946 Chapter 3). This was due to increase in blood flow through the muscles which must have been at least doubled. In spite of the rise in general blood pressure intravenous infusions of noradrenaline do not increase the blood flow through muscle (Duncanson Stewart and Edholm 1949 Barcroft and Konzett 1949 Barnett et al 1950).

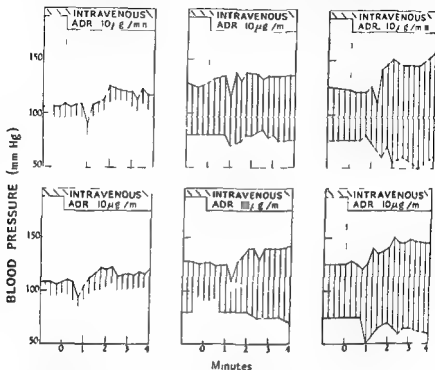
One of the large individual circulations is that through the brain. The effects on it of adrenaline and of noradrenaline have been studied by King Sokoloff and Wechsler (1952) by the nitrous oxide and internal jugular venous blood sampling method. Adrenaline increased the flow by approximately 50 per cent. Noradrenaline caused constriction the average decrease in flow was 10 per cent.

The changes in the different organs have been collected together in Table VIII and afford independent evidence not inconsistent with the findings previously described namely that adrenaline stimulates the cardiac output whereas noradrenaline does not. They show that the overall vasodilator action of adrenaline is essentially due to its effect on the circulations in the liver and skeletal muscles.

TABLE VIII

	Blood flow		Dose		
	Adrenaline		Noradrenaline		
	ml/min	ml/min	mg	ml/min	mg
Liver	1500	3000	100	1700	0
Kidney	1000	900	40	1200	-20
Skeletal muscles	1000	2000	100	1000	0
Brain	70	900	20	67	-10
	4750	6800	40	435	-8

Finally it is of interest to compare the actions of the two amines on the blood pressure in man the cat the dog and the rabbit. It will be seen that differences still need to be explained. In animal experiments the hormones have usually been injected and not infused so that the corresponding effects



Minutes

Fig 93 Experiments showing that the first effect of intravenous infusion of adrenaline on the human arterial blood pressure is to cause a small transient decrease

The blood pressure records were made every  $\frac{1}{4}$  min by the auscultatory method (Allen, Barcroft and Fiholm 1946)

in man will be those taking place at the very beginning of an infusion before the establishment of equilibrium. Careful measurement of the human arterial blood pressure by the auscultatory method usually reveals a small transient decrease before the sustained rise. This may be seen in Fig 93. This transient decrease is readily displayed by the intra-arterial manometer (Barnett et al). In this connection it is worth noting that infusions of adrenaline into a normal subject

never cause a sustained fall in pressure however great the dilution. The transient fall in the human blood pressure probably corresponds to the fall seen following the injection of small doses in the cat (Cannon and Lyman 1912) and dog (Hoskins and McClure 1912; Lands, Luduena, Ananenko and Crant 1950). This is apparently unobtainable in the rabbit (Cannon and Lyman). With noradrenaline the situation is different. In man the capacitance manometer shows that it causes a simple rise in pressure (Barnett et al.) this is so in the cat too (Meier Gross and Eichenberger 1949) but oddly enough noradrenaline causes a fall in pressure in the dog (Lands et al.). As far as we are aware the response in the rabbit has not been studied. The explanation of these differences though of great fundamental interest is not at present known.

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## CHAPTER 10

### ADRENERGIC BLOCKADE

In 1906 Dile found that large doses of preparations of ergot of rye paralysed the excitor function of the sympathetic nerves and also of adrenaline. These observations were the basis of the considerable volume of work on adrenergic blockade and adrenergic blocking agents which has been carried out since then. Adrenergic agents are the natural amines adrenaline and noradrenaline which induce the responses of the great majority of the sympathetically innervated effector cells.

Adrenergic blocking agents are those substances which specifically inhibit certain effects of adrenaline noradrenaline and sympathetic nerve stimulation. The terms sympatholytic and adrenolytic should not be used for in general

neither nerve ending nor mediator nor effector cell is lysed by these agents (Nickerson 1949). It should also be clear that adrenergic blockade refers to an action at the neuro-effector junction that is a peripheral effect. Other actions on the efferent vasomotor pathway are by definition not part of this topic. Nevertheless many adrenergic blocking agents cause vascular changes not due to their adrenergic blocking properties and we must endeavour to distinguish between these effects and true adrenergic blockade.

There are four main groups of adrenergic blocking agents and in this chapter we will consider their action in man so far as it is at present known. The effects of the alkaloids of ergot will be discussed in rather more detail than the other substances not only because we have investigated them to a greater extent than the other agents but also because we may make certain generalizations which are applicable to all adrenergic blocking agents to varying degrees.

#### 1 *Hydrogenated Alkaloids of the Ergotoxine Group*

Although the anti-adrenaline properties of the ergot extracts was recognized in 1906 the toxic effects of vasoactive doses prevented any serious investigation of the circulatory effects of ergot in man. The principle of ergot which possessed the

greatest vascular activity (ergotoxine) also caused the most adverse side effects. Stoll and Hoffman (1943a) showed that ergotoxine is made up of three separate alkaloids: ergocornine, ergocristine and ergocryptine. The same workers (1943b) found that the lysergic acid molecule which is a component of each alkaloid could be hydrogenated to form new and stable substances. These compounds known as dihydroergocornine, dihydroergocryptine and dihydroergocristine (the dihydro alkaloids) were much less toxic than the natural alkaloids yet retained certain anti-adrenaline properties.

Because of the diminished toxicity the dihydroalkaloids were extensively investigated in man. Dihydroergocornine (DHO 180) was studied by Bluntschli and Coetz (1947), Freis, Stanton and Wilkins (1948) and others. Less attention was given to the effects of mixtures of the dihydro alkaloids or to the effects of dihydroergocryptine or dihydroergocristine probably because dihydroergocornine displayed the greatest vascular activity. The majority of these investigators made little attempt to interpret the action of the dihydro alkaloids describing many effects as evidence of the sympatholytic or adrenolytic properties of the compounds. It is clear that not all of these effects would come within the more rigid definition of adrenergic blockade set out at the beginning of this chapter.

Barcroft, Konzett and Swan (1941) investigated the effect of dihydroergocornine and of a mixture of equal parts of the three dihydro alkaloids (Hydergine) on the human peripheral circulation. They measured peripheral blood flow with the plethysmograph and found that either dihydroergocornine or Hydergine infused intravenously caused an increase in the blood flow in the hand and foot in all of ten normal subjects. Fig 10.1 is from their paper. This confirmed the observations of Coetz (1949) who measured the finger blood flow and Hayes et al (1949) who measured the blood flow in the whole limb. Barcroft et al found little change in the calf blood flow in normal subjects.

The cause of the dilatation in the hand and foot was considered. Goetz (1949) had concluded that the dilatation was due to central inhibition of sympathetic vasoconstrictor tone and not to peripheral adrenergic blockade but his evidence did not exclude an adrenergic blocking effect. Goetz concluded

that the dilatation seen in normal limbs was due to a central depression of vasoconstrictor tone because sympathectomized limbs fail to dilate. He assumed that if the alkaloids dilated normal vessels by a peripheral action they should also cause dilatation in sympathectomized vessels. This does not necessarily follow for a substance which blocks the adrenergic

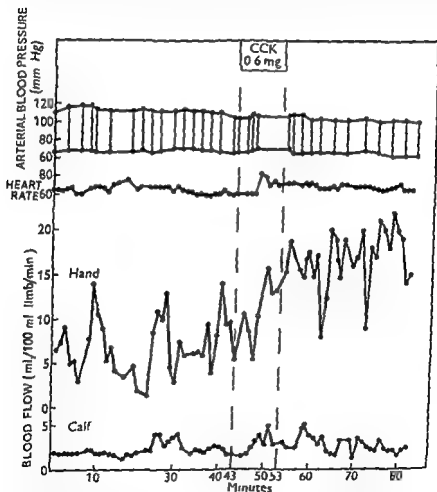


Fig 10.1 Results showing that alkaloids of the ergotamine group cause vasodilatation in the hand

In this experiment Hydergine (CCK) was administered intravenously. It is a mixture of equal parts of dihydroergocornine (DHE) and dihydroergocristine and dihydroergocryptine (Barcroft, Konzett and Swan 1951).

transmitter of sympathetic nerves in normal limbs might not cause vasodilatation in sympathectomized vessels. In such limbs vascular tone may not be due to the action of adrenaline but to that of some quite different mechanism (Chapter 7).

Vasodilatation in the hand due to pharmacological agents can result from inhibition of constrictor tone at a number of

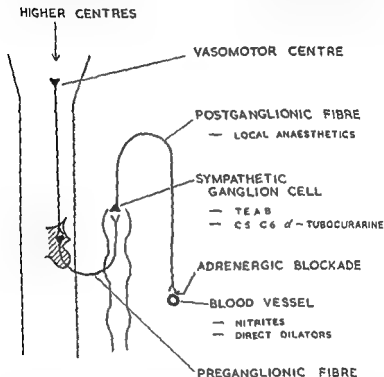


Fig 10.1 Diagram showing sites of inhibitory action of drugs on sympathetic vasoconstrictor tone

points along the sympathetic efferent pathway or from a direct effect on the blood vessels. This is shown diagrammatically in Fig 10.2. We do not need to consider activity of dilator nerves—because these do not exist in the hand (Arnott and Macfie 1948).

Firstly an attempt was made to see if the dihydro alkaloids had a peripheral action. This was done by recording the blood flow in both hands and then infusing the alkaloid directly into



the brachial artery on one side. Fig 10 3a shows that the intra arterial infusion of 0.2 mg dihydroergocornine caused an increase in blood flow in the ipsilateral but not in the contra lateral hand. A similar response was obtained in ten other subjects. This indicates that the dihydro alkaloids either

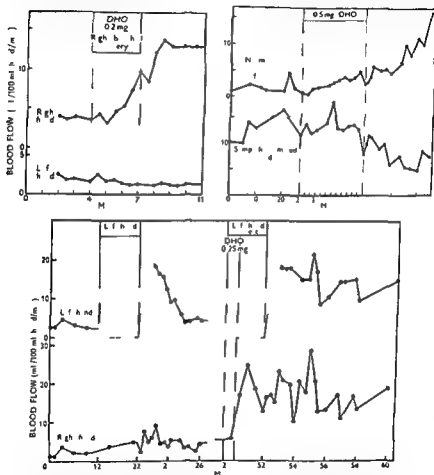


Fig 10.3 Results described fully in the text revealing two distinct vasodilator actions of the alkaloids of the ergotoxine group on the blood vessels of the hand.

(1) Low concentrations as have to be used in intravenous experiment to avoid toxic effects have little of the peripheral blocking action and release sympathetic tone by a powerful central inhibitory action.

(2) High concentration as can be used in intra arterial experiments exert a true local adrenergic blocking action and release sympathetic vasoconstrictor tone peripherally. (Harcroft & Swett and Swan 1951)

block the tonic constrictor impulses arriving by way of the sympathetic nerves—or otherwise cause a vasodilatation by their direct action on the walls of the blood vessels. To decide between these two possibilities we investigated the action of the dihydro alkaloids on sympathectomized limbs for if dilatation occurred in the sympathectomized limb one could conclude that the alkaloids caused a relaxation of the blood vessels. This was not found to be the case. While there was no significant change on intravenous administration of the alkaloids in four subjects (Fig. 10.3b) intra arterial infusions actually caused a vasoconstriction in two subjects. Therefore the vasodilatation seen on intra arterial infusion of the dihydro alkaloids in normal limbs was due to blocking of the tonic constrictor impulses mediated by the sympathetic nerves—true adrenergic blockade.

It does not necessarily follow however that the vasodilatation seen after intravenous infusions in normal subjects is due to the same mechanism. Although the dihydro compounds are less toxic than the natural alkaloids of ergotamine they still retain certain unpleasant side effects which limit the dose which can be given. Barcroft et al. were unable to give very large doses of the dihydro compounds intravenously and clearly the amounts given intra arterially are much larger than the amount reaching the hand following intravenous administration. The following experiment was therefore devised to see whether central inhibition of vasoconstrictor tone—as suggested by Goetz—was responsible for the peripheral dilatation after intravenous administration (Fig. 10.3c).

The resting blood flow was determined in both hands of a normal subject. Then the flow in the left hand was occluded by a cuff for 10 minutes after which the resultant period of reactive hyperaemia was recorded. After a suitable period of rest the circulation in the left hand was again occluded for 10 minutes but during the first 3 minutes of this period dihydroergocornine was given intravenously. The blood flow in the unoccluded right hand increased in the usual manner. Now the dihydroergocornine reached the adrenergic nerve endings in the right hand but not in the left hand. Pothlin (1947) had observed that in the rabbit 99 per cent of the dihydro alkaloids were removed from the circulation in 5 minutes. We

considered that little if any dihydroergocornine would remain in the blood when the circulation in the hand was released. On release of the occlusion on the left hand the peak of reactive hyperemia passed off but the blood flow did not return to its previous value—there was a persistent vasodilatation of almost the same degree as in the right hand. This must have been due to inhibition of sympathetic vasoconstrictor tone centrally. The question arises as to whether inhibition could have been caused in the sympathetic ganglia. This appears to be unlikely for Konzett and Rothlin (1950) found no such action on the perfused superior cervical ganglion of the cat. Also the occurrence of nausea and vomiting as side effects of the dihydro substances suggest a medullary action. Therefore we conclude that the hydrogenated alkaloids of the ergotoxine group have an adrenergic blocking action in man when given in relatively large doses by the intra arterial route. When given intravenously however the adrenergic blocking effect is small and the vasodilatation is in the main due to central inhibition of sympathetic vasoconstrictor tone as suggested by Goetz (1949).

Barcroft et al (1951) then investigated the effects of the alkaloids on the response to infusions of adrenaline and noradrenaline for substances which block sympathetic nerve endings are said to be more effective against circulating sympathomimetics. Fig 10.4 shows an experiment in which short infusions of adrenaline and noradrenaline were given before and after the intravenous administration of Hydergine. It indicates that the dihydro alkaloids had very little effect on the arterial blood pressure or heart rate response to adrenaline or noradrenaline. The constrictor action of adrenaline on the skin vessels and of noradrenaline on the skin and muscle vessels was not affected. From this and five other similar experiments Barcroft et al concluded that the dihydro compounds had no blocking action on the effects of adrenaline and noradrenaline. In this respect their results differed from those of Goetz and Katz (1949) who described reversal of the adrenaline pressor effect after intravenous dihydroergocornine and from those of Kappert (1949) who concluded that dihydroergocornine reversed the constrictor action of adrenaline on the skin vessels. We are unable to account for these differences.

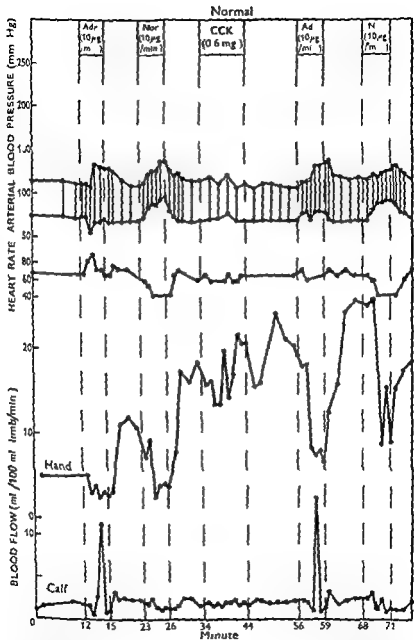


Fig 10.4 Results showing effect of a large intravenous dose of hydrogenated alkali of the ergotamine group (Hytergin) almost enough to cause toxic symptoms of 1 to block the vasoconstrictor action of adrenaline and noradrenaline in the hand (Barcroft, Konzett and Swan 1951)

Adrenaline and noradrenaline given intravenously act upon organs and structures which are almost unaffected by the direct action of the intravenous dose of the dihydro alkaloids. It is therefore difficult to see how a strong anti adrenaline effect should have been obtained from doses of alkaloid which when given intravenously act in the main centrally.

Regarding the effect of the dihydro alkaloids on the pressor response to adrenaline Goetz and Katz (1949) reported that adrenaline caused a fall in blood pressure when given after dihydroergocornine. But Barcroft et al (1951) were unable to confirm this. An explanation of this divergence of response might be that while in Barcroft et al's experiments the subject lay supine with one pillow under the head the other investigators may have placed their subjects in a more upright position. If the posture is altered fundamental cardiovascular dynamics are affected and differing results may be obtained. This is all the more true when vasodilator substances have been given and may be responsible for the fact that Barcroft et al found that the dihydro alkaloids failed to lower the blood pressure in normal subjects although a hypotension was reported by several other workers.

Barcroft et al also investigated the effects of Hydergine given intra arterially on the constrictor response in the foot to adrenaline and noradrenaline. The observations made did not indicate any blocking effect to adrenaline or noradrenaline but they thought that the doses of sympathomimetics used might have exceeded the normal physiological range for man. Swan (1951a) studied this aspect of the problem in more detail using the hand for his investigations. Definite constriction occurred in most subjects at a dose rate of  $\frac{1}{2}$   $\mu$ g adrenaline or noradrenaline per minute when given into the brachial artery. Constriction in the hand was also recorded on immersing one foot in water at 12 C. The cold constrictor response so obtained is mediated by the sympathetic pathway and is a convenient way of testing sympathetic constrictor tone. Then dihydroergocornine 0.1 to 0.25 mg was given intra arterially and the ensuing response to intra arterial adrenaline or noradrenaline or to the cold constrictor test was observed. Fig 10.5 is an example in which the constrictor effect of noradrenaline and of the cold stimulus are compared before and

after the dihydro alkaloid. It will be seen that the constrictor response to  $\frac{1}{2}$   $\mu$ g noradrenaline and to cold were abolished by the dihydro alkaloids and the response to  $\frac{1}{2}$   $\mu$ g noradrenaline is very slightly reduced. The same observations were also made with respect to adrenaline. The blockade so produced can be overcome by larger doses of adrenaline or noradrenaline.

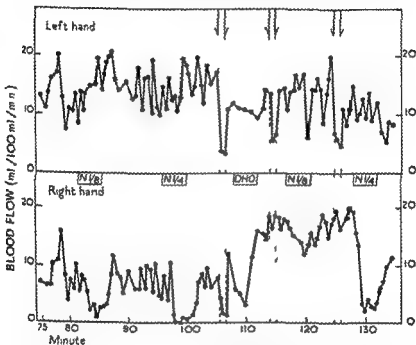


Fig 10. Given intra-arterially reaching the right hand in high concentration dihydroergocorn (DHO) blocked the peripheral vasoconstrictor action of a small dose of noradrenaline ( $\frac{1}{2}$ ) and also that induced reflexly by placing the feet in cold water (between pairs of vertical broken lines).

it has been present up to 30 min after the dihydro alkaloids were given. The effect of the dihydro alkaloids on the adrenaline and noradrenaline effect on the muscle blood vessels is variable—but in general the response is unchanged.

We are not in this work concerned with the overall effects of the dihydro alkaloids on the circulation. An adrenergic blocking action has been conclusively demonstrated—but as we have already pointed out the effects observed must be

critically interpreted. The responses in the intact organism are complex representing the sum of local and general effects. At times the local effect may be marked. Grayson and Swan (1950) found that local injection of the dihydro alkaloids into human colonic mucosa exposed at colostomy caused a vaso dilatation. Yet when the alkaloids were given intravenously a vasoconstriction occurred in the colonic mucosa.

To summarize the position in regard to the effects of the hydrogenated alkaloids in the human peripheral circulation we may say that although in large amounts they produce true adrenergic blockade toxic effects permit the general administration of doses which only cause vasodilatation by a central inhibition of sympathetic vasoconstrictor tone.

## 2 *The Benzodioxanes*

Although these blocking agents have a relatively weak action in comparison to others one of their number is of considerable interest in man—because it is used in the diagnosis of pheochromocytoma of the adrenal gland. The several members of this series fall into two different types and are designated by a numeral followed by the letter F (Fournier—who synthesized the series). Those substances which are more effective against the effect of sympathetic stimulation than against circulating adrenaline and noradrenaline are typified by the compound 833F while those which are more effective against circulating adrenal hormones are represented by the compound 933F. The adrenergic blockade produced by the benzodioxanes in animals is weak when compared to other substances. There are many aspects of sympathetic and humoral action which are not affected by them. Finally these compounds are the only adrenergic blocking agents which accelerate the inactivation of adrenaline (Morrison and Lissak 1938).

In 1947 Goldenberg, Snyder and Aranow described the benzodioxane test for pheochromocytoma. In this test 25 mg 933F per kilogram body weight is injected intravenously. If the arterial blood pressure is elevated due to the presence of circulating pressor hormones then a fall in blood pressure of 10-15 mm duration is observed but if the case is one of essential or renal hypertension then the blood pressure usually rises slightly. This test is now of proven value in the diagnosis of pheochromocytoma. In their original

paper Coldenberg et al (1947) reported an investigation in which continuous infusions of adrenaline were given to normal subjects. When the blood pressure was stable 933F was injected intravenously producing a fall in blood pressure.

From Goldenberg's experimental results it would appear that 933F was either blocking the augmentor effect of adrenaline on the cardiac output or was lowering further the already diminished total peripheral resistance. From animal experiments the former possibility appeared unlikely (de Vrieschhouwer 1947). It occurred to Prunty and Swan that plethysmographic determination of limb blood flow might assist in the interpretation of the action of 933F on the overall peripheral resistance. The latter workers also investigated the effect of 933F on the hypertension produced by infusions of noradrenaline in normal subjects.

Prunty and Swan (1950) measured calf and hand blood flow in normal subjects lying supine with the head elevated 15° to the horizontal. The blood pressure was measured with the sphygmomanometer. Continuous infusions of adrenaline or noradrenaline were given and the vascular response recorded for about 20 minutes by which time the circulatory changes had stabilized. Then a dose of 0.1 mg 933F per kilogram body weight was slowly injected either directly into the tube through which the adrenaline or noradrenaline infusion was being maintained or, in some subjects, was injected into another suitable vein. The ensuing responses were noted the infusion of adrenaline or noradrenaline being maintained.

An experiment in which a continuous adrenaline infusion was given is shown in Fig. 10.6. The adrenaline infusion increased the systolic blood pressure while the diastolic pressure declined. The calf blood flow is increased. At the arrow 15 mg 933F was injected over about 90 sec. This resulted in a brisk increase in heart rate and an intense flushing of the face and neck. There was a further increase in calf blood flow. The diastolic blood pressure fell further but recovered to its previous value within a few minutes. The systolic pressure also declined slightly but then rose to a maximum value of 180 mm Hg. There was a moderate but gradual fall in blood pressure for the remainder of the adrenaline infusion. This subject did not complain of symptoms other than palpitation. Most subjects



however experienced a metallic taste in the mouth—with severe palpitations a burning sensation in the face and neck pulsations in various parts of the body and a sense of alarm. One subject (No. 6) experienced symptoms suggestive of an

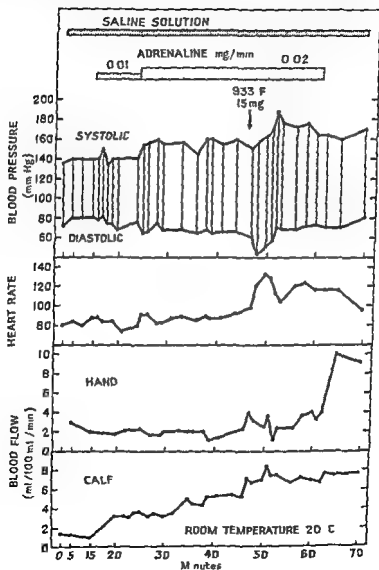


Fig. 106 Result showing failure of benzol xane (933F) to block the hypertensive action of adrenaline (Prunty and Swan 1950)

**TABLE IX**  
*Blood pressure as heart rate*

Subject	Age yr	Sex	Diag	Basal	3 m before 933F	1 m after 933F	3 m after 933F	10 m after 933F
1	45	M	B P Pulse	130 0 88	122/74 110	138/ 122	160/76 132	168/80 110
2	3	M	B P Pulse	130 80 80	158/72 90	158/40 120	170/55 118	175/68 120
3	6	M	B P Pulse	135 80 80	155/56 88	145/45 104	158 65 112	175 68 104
4	23	M	B P Pulse	140 80 86	155/66 72	155 40 112	190 60 100	175 68 104
5	8	M	B P Pulse	115 0 66	150/66 90	174/60 138	174 0 114	116 0 104
6	23	M	B P Pulse	155 75 86	145/106 64	145 98 96	245 104 68	175 108 66
7	7	M	B P Pulse	125 80 88	184/104 68	200 75 140	190 80 108	180 80 96
8	35	M	B P Pulse	120 80 88	156/105 86	170 60 116	170 90 104	165/85 78
9	9	M	B P Pulse	130 5 60	170/100 88	168 68 45	160 55 44	170 75 48

encephalopathy Table IX shows the response of blood pressure and heart rate in nine normal subjects of whom five received adrenaline and four noradrenaline. It was thought that apart from subject No 11 no significant fall in blood pressure had been demonstrated. In the peripheral circulation an increase in blood flow occurred after the injection of 933F in both hand and calf.

The results reported above were at variance with those of

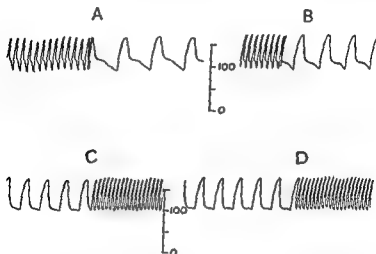


Fig 10.7 Record showing that benzodioxane (933F) probably increases cardiac output

Intra arterial tracings of the blood pressure in the brachial artery during the continuous intravenous infusion of adrenaline at the rate of  $10 \mu\text{g/min}$ . A B before C D after intravenous injection of  $1.0 \text{ mg}$  benzodioxane (933F). After the 933F the pressure falls more rapidly during diastole and the heart rate increases. This implies a decrease in total peripheral resistance and an increase in cardiac output.

Goldenberg et al (1947) and Goldenberg and Aronow (1950) insofar as Prunty and Swan did not consider the responses they obtained could be regarded as depressor. How can this difference be explained? Firstly it must be remembered that the blood pressure is a balance between the cardiac output and the total peripheral resistance. Although Prunty and Swan did not measure the cardiac output they thought that it was increased. Pulse contour tracings obtained with a sensitive capacitance manometer (Fig 10.7) supported this. The increased cardiac output was considered to overcompensate for

the undoubted peripheral vasodilatation and so a rise in systemic arterial pressure soon occurred. Now posture may play a considerable part in determining vascular responses because it will affect the distribution of blood in the veins the right auricular pressure and other variables. It is possible that this factor is at least in part responsible for the different results obtained by Prunty and Swan and also by Freis et al (1951). It is difficult however to describe the short hypotension produced by 933F as evidence of adrenergic blockade.

Using the intra arterial infusion techniques Swan (1951b) investigated the effect of 933F on the blood flow in the hand and also on its effect on adrenaline and noradrenaline vasoconstriction. Briefly—2 mg 933F given intra arterially caused a moderate increase in blood flow of 5–11 minutes duration in six normal subjects. But almost the same vasodilatation was observed in two sympathectomized limbs when 933F was given intra arterially. This suggested that 933F in these doses has in part at least a direct dilator effect on blood vessels. Further experiments are needed to prove this point.

If an injection of 1–2 mg 933F was made during an infusion of adrenaline or noradrenaline in intra brachial doses up to  $0.1 \mu\text{g}$  per minute a transient abolition of the vasoconstriction was seen. The constrictor effect of infusions of  $\frac{1}{2} \mu\text{g}$  per minute adrenaline or noradrenaline was reduced by the prior injection of 1–2 mg 933F. Small doses of 933F (0.1 mg to 0.5 mg) had little effect on the adrenaline or noradrenaline vasoconstriction although they did cause some increase in blood flow.

These results at present incomplete indicate that 933F in large doses has a weak adrenergic blocking action in man. They do not however explain the action on the arterial blood pressure described by Goldenberg et al (1947) and Goldenberg and Aranow (1950).

#### ■ *Priscol*

This substance is an effective vasodilator in doses which may be given to the human subject. The side effects with large doses include tachycardia flushing and conjunctival injection. We have had little experience of its use in this laboratory but our findings agree in general with those of Wakim et al (1950).

Our observations are reported only to indicate future problems to be dealt with

We have seen vasodilatation in effectively sympathectomized limbs thus confirming Grimson et al (1948) In addition we have investigated the effects of intravenous infusions of adrenaline and noradrenaline on the peripheral blood flow finding that the constrictor effect in the skin (and in the case of noradrenaline in muscle) is much reduced after 50 mg priscol given intravenously The blood pressure response to the circulating sympathomimetics is unchanged

#### 4 *Dibenamine*

This substance is probably the most effective adrenergic blocking agent available (Nickerson and Goodman 1947) It has not been the subject of extensive investigation in man apart from that reported by Hecht and Anderson (1947) These workers reported that dibenamine inhibited the pressor effects of adrenaline and the pressor response to cold One of the difficulties in the study of the effect of dibenamine in normal subjects is the duration of its action Orthostatic hypotension may last for hours after effective doses of dibenamine The use of intra arterial technique should overcome this obstacle to experimental investigation

#### *Summary*

Adrenergic blocking agents are those substances which specifically inhibit the response of the effector cell to the sympathetic transmitter and to circulating sympathomimetic agents All the groups of substances which produce adrenergic blockade in animals can be shown to do so in man also However the dose required to be effective by the intravenous route is frequently not tolerated because of unpleasant side effects so that only in the case of dibenamine and perhaps priscol has true adrenergic blockade been demonstrated on intravenous administration The hydrogenated ergotoxine alkaloids and 9331 have a blocking action when given in relatively large doses intra arterially

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## CHAPTER 11

### PHAEOCHROME TUMOURS

Recent advances in our knowledge concerning the nature of the transmitter agents of the sympathoadrenal system has led to better understanding of the effects of these substances in man. A condition which gives rise to an excessive liberation is a secreting tumour of the adrenal medullary tissue. The majority of such tumours lie in or near the suprarenal glands but also arise in para aortic rests of medullary tissue. The tumours are usually benign adenomata but about 10 per cent are malignant. They are known as phaeochromocytomata and are commonly unilateral in 12-15 per cent of cases more than one tumour is present.

Until recently phaeochromocytoma was thought to be a rare condition but it is now clear that if the possibility of medullary tumour is considered in certain hypertensive patients unsuspected cases may be diagnosed. In all 270 cases had been reported up to 1949 of which 67 per cent were proven post mortem (Smithwick et al 1950). Early diagnosis and surgical removal frequently results in complete recovery of normal health. Therapeutic advances now permit more accurate diagnosis of the condition and have reduced the operative mortality thus a more favourable prognosis may be given. We will therefore consider the clinical aspects of the condition and discuss this sole example of disordered physiology of adrenal medullary function.

A reasonable concept of the role of adrenaline and noradrenaline in the body would be to ascribe the sympathetic transmission to the latter and emergency adrenal medullary function to the former. It is probable that the adrenal medulla discharges an effective amount of adrenaline into the circulation during stress. Although the natural secretion of the adrenal gland contains up to 70 per cent noradrenaline the mixture will have the effect of adrenaline (de Largy et al 1950). But in phaeochromocytoma this function is disordered. Firstly large amounts of the medullary hormone are released into the

circulation. The quantities liberated are far in excess of the need during emergency and cause responses which are harmful. Also the predominant hormone liberated from phaeochromocytoma is not always adrenaline for excess of noradrenaline may be found. Noradrenaline does not further the response to emergency—indeed its actions antagonize adrenaline in many respects. Finally in a large number of cases there is evidence of a liberation of excessive amounts of medullary hormone over a long period of time which is in contrast to the intermittent response to stress.

The majority of patients suffering from phaeochromocytoma present symptoms referable to their hypertension but sometimes metabolic symptoms predominate. A tentative classification is as follows

(A) *Hypertensive Group*

- 1 Paroxysmal hypertension—sympathico adrenal syndrome
- 2 Elevated resting blood pressure—paroxysmal hypertension superimposed
- 3 Sustained hypertension in many aspects similar to essential or malignant hypertension but certain metabolic signs are present
- 4 Sustained hypertension identical with essential hypertension

(B) *Metabolic Group*

- 1 Glycosuria elevated metabolic rate and sustained hypertension
- 2 Metabolic symptoms episodes of paroxysmal hypertension

1 Paroxysmal hypertension. This syndrome is characterized by sudden attacks consisting of palpitation nausea and sometimes vomiting headache substernal pain pallor of the face and extremities and tremor (Mackeith 1944). At times fear out of proportion to the severity of the attack occurs.

The symptoms may be quite mild or of great severity—indeed the patient may die during or after an attack. The duration of the attack is commonly about one hour—but frequently attacks last only a few minutes. They may recur daily or only at intervals of months and may alter in severity. If the patient is seen during an attack pallor of the face and



extremities will be noted while the general condition will vary with the severity of the attack. The systolic blood pressure is sometimes 300 mm Hg and there is also a diastolic hypertension. The blood pressure frequently varies during the attack. The radial pulse is usually hard, the rate varies from patient to patient. In several patients extreme bradycardia has been noticed during the attack. The extremities are cold and blanched but usually moist. Sweating is common during the attacks, at times streams of sweat course down the patient's face and trunk while the hands and feet are relatively dry. The mouth temperature is usually elevated during a paroxysmal attack. Urinary examination frequently reveals glycosuria. The paroxysm may terminate fatally by reason of acute pulmonary oedema or cerebral haemorrhage. Otherwise the patient suddenly becomes aware that his unpleasant symptoms are diminishing. Sweating may persist and indeed increase while flushing of the face and extremities is common. The flushing may be associated with a sensation of warmth spreading over the neck and face. The blood pressure falls rapidly to normal or subnormal values. In some cases this fall may be extreme and ultimately fatal. For a more complete account see Mackenth (1944).

2 A number of patients have been seen in whom the resting blood pressure level is high and who suffer from further paroxysms of hypertension superimposed upon a symptomless hypertensive state. They may represent an intermediate group between 1 and 3 and are separated here from the other groups because they represent a different diagnostic problem.

3 Patients with sustained hypertension closely resembling essential hypertension and without evident paroxysms of hypertension. This group probably contains the greatest number of patients suffering from phaeochromocytoma. Green (1946) reviewed 51 adequately reported cases which he selected from the literature and observed that 70 per cent had suffered from sustained hypertension during life.

The patients may have mild or severe hypertensive symptoms or may at times exhibit signs consistent with malignant hypertension. The differentiation of the rare phaeochromocytoma from the common essential hypertension is therefore a problem to test the diagnostic skill of the

physician. In the majority of these cases however symptoms and signs are present which may suggest the correct diagnosis. The most important of these is excessive sweating. Smithwick et al (1950) reported that this symptom occurred in only 2 per cent of patients with essential hypertension but in 9 out of 10 patients with phaeochromocytoma. Symptoms referable to a vasospastic condition of the hands and a raised mouth temperature were also reported by many patients with phaeochromocytoma—but were uncommon in essential hypertension. A raised basal metabolic rate, glycosuria and an elevated fasting blood sugar also occur more frequently than in essential hypertension.

4 Patients with sustained hypertension without any symptoms suggestive of adrenal medullary dysfunction. This variety is uncommon and usually is drawn from post mortem material. Although the symptoms during life may have been inadequately noted in some cases it seems clear that some patients with a medullary tumour die in cardiac failure without any symptoms referable to the tumour.

5 Glycosuria, elevated metabolic rate and sustained hypertension. In some patients the metabolic symptoms may predominate and when weight loss is extreme an endocrine disturbance is suggested. When a high fasting blood sugar is discovered diabetes mellitus may be considered. A good example of this variety is the case reported by Raab and Smithwick (1949).

6 In a small minority of patients metabolic symptoms and signs predominate while the blood pressure remains normal. Paroxysmal hypertension only occurs. These patients are usually considered to have other endocrine disorders.

#### ADRENALINE, NORADRENALINE AND PHAEOCHROMOCYTOMA

It is certain that both adrenaline and noradrenaline are present in excess in the blood of patients suffering from phaeochromocytoma. Holton (1948) and Goldenberg et al (1949) have reported large quantities of both amines in tumours following surgical removal while Engel and Euler (1950) have demonstrated large quantities of adrenaline and noradrenaline in the urine of such patients. We discussed in earlier chapters information obtained from infusions of adrenaline and

noradrenaline in normal subjects. Are the symptoms and signs in patients similar to the laboratory findings on infusion of the amines in normals? In certain important respects this is not so. The probable explanation of the discrepancy lies in the differing rates in which the hormones enter the circulation. In phaeochromocytoma enormous quantities are liberated and effects are therefore seen which could not be deliberately induced in normal subjects nor indeed tolerated by them.

We will therefore discuss the signs and symptoms of phaeochromocytoma in regard to the known action of adrenaline and noradrenaline in man and consider the discrepancies which exist.

Both adrenaline and noradrenaline cause the normal subject mental disturbance, adrenaline to a greater extent than noradrenaline. This varies from subject to subject—but on two occasions subjects who had previously had adrenaline reported their sense of alarm to be much greater with noradrenaline. Palpitation and tachycardia as caused by adrenaline or bradycardia (Barnett et al. 1950 case 3) as with noradrenaline have been reported in patients. The tremor, weakness and fatigue common in patients are all seen on infusion of adrenaline in normal subjects. A symptom of interest is the excessive sweating which is a feature of phaeochromocytoma. We have never seen sweating in some 300 infusions in normal subjects. The sweating in phaeochromocytoma has been attributed to a retention of heat owing to the cutaneous vasoconstriction. But there are reasons for believing that this may not always be so. Many cases have been reported in which profuse sweating occurred within a few seconds of the appearance of pallor and frequently in association with headache. Also it is strange that we have never seen sweating in normals in spite of long infusions which caused sustained pallor and presumably considerable heat retention. It seems likely that hypothalamic stimulation may be responsible for this symptom. Swan (1951a) observed that sweating persisted for a week after removal of a tumour.

Flushing and vasomotor collapse have been reported following hormonal discharge. The flushing is probably similar to that seen following the end of an adrenaline infusion. Smithwick et al. (1950) also thought that a heat retention mechanism

might underlie this response. But adrenaline causes a central inhibition of vasoconstrictor tone (Swan 1951b). This is not thought to be due to heat retention for although vasodilatation in the hand was found to follow 20  $\mu$ g adrenaline for 3 min it occurred only infrequently after 10  $\mu$ g for 10 min.

A more extreme response probably of the same nature as the hypotension observed after doses of 100  $\mu$ g per minute (Green et al 1948). Collapse is not infrequently seen both during the course of the disease or after removal of the tumour at operation. This collapse may be transient due to inhibition of vasomotor tone and will respond well to intravenous noradrenaline. But at times an irreversible effect is produced. Hypotension, anuria and death may result in spite of heroic efforts at medication. This latter state corresponds to the adrenaline shock seen in animals after massive doses of adrenaline (Viggran and Feyer 1949).

The changes in blood pressure and overall haemodynamics are of considerable interest. Briefly both adrenaline and noradrenaline increase the systolic blood pressure in normal subjects but whereas noradrenaline also elevates the diastolic pressure adrenaline usually causes no change or a slight fall in the diastolic pressure. We have seen a rise in diastolic pressure only occasionally with moderate doses of adrenaline in normals. Goldenberg et al (1948) observed that while noradrenaline increased the total peripheral resistance moderate doses of adrenaline caused an overall vasodilatation. Now patients with phaeochromocytoma have always a high diastolic pressure if they are in a hypertensive state and the superficial evidence pointed to a raised total peripheral resistance. This suggested to Prunty and Swan (1950) that it was likely that noradrenaline and not adrenaline caused the hypertension. But it is now clear that this is not the case for tumours containing predominantly adrenaline have been removed from patients who had considerable elevation of the diastolic pressure. Whereas small doses of adrenaline cause an overall vasodilatation larger amounts such as occur in phaeochromocytoma must cause an overall increase in peripheral resistance (Goldenberg et al 1950) a concept of adrenaline action in keeping with observations made in the dog and cat. There is some direct evidence for this action in man. Whereas small doses

of adrenaline given intra arterially cause little change in the calf blood flow doses greater than 6  $\mu$ g per minute cause a definite reduction in blood flow (Swan 1951). Therefore it is clear that both amines can cause a rise in diastolic blood pressure and an overall vasoconstriction.

Increased oxygen consumption and an elevation of the blood sugar have been reported to follow adrenaline infusion. With noradrenaline the metabolic effects are much less. Reale et al (1950) found no alteration in the oxygen consumption during infusions of noradrenaline in normals. This might lead one to suppose that patients who exhibited metabolic symptoms might have tumours containing predominantly adrenaline. But this is not the case for high fasting blood sugar levels and raised metabolic rate have been observed in patients with 88 per cent and 97 per cent noradrenaline tumour contents (Goldenberg et al 1950 cases 13 and 12). We must therefore conclude that at high dose levels noradrenaline influences metabolism by either a direct or indirect action.

This discussion has so far centred around the production of the main symptoms and signs in phaeochromocytoma by the action of adrenaline and noradrenaline. We will now concern ourselves with the clinical classification of the condition as suggested in the beginning of this chapter. We divided the condition into those presenting with predominantly hypertensive symptoms and signs and those with hypermetabolic manifestations.

The former group shows the development of a definite pattern of hypertension. Thus some patients exhibit paroxysmal hypertension (Group I) others have an elevated basic pressure on which an additional paroxysmal hypertension is clearly superimposed (Group II). The majority of patients have clear evidence of sustained hypertension with indefinite evidence of further paroxysms of hypertension (Group III) and finally a minority of patients die from a hypertension in no way different from essential hypertension (Group IV).

Let us suppose that in the natural history of an adrenal medullary tumour the discharge of hormone is at first paroxysmal but after some time a small continuous basal liberation is established with superimposed paroxysmal discharge occurring from time to time. Gradually the basal secretion

may increase with a progressive diminution of the effects of paroxysmal hormonal discharge. This is a reasonable view to take as the level to which the blood pressure can rise with survival of the patient is reduced with the progressive elevation of the basal blood pressure and paroxysms of great intensity are not likely to be frequent. Finally it is possible that a state may be reached in which further production of medullary

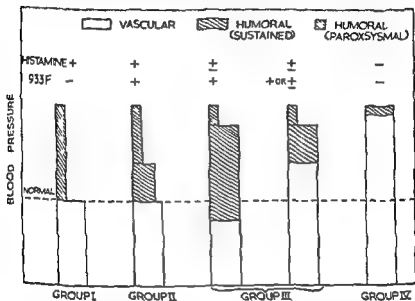


Fig 111 Classification of phaeochromep tumours according to the relative amounts of humoral paroxysmal, humoral sustained and essential (vascular sustained) hypertensive element.

The relative importance of the paroxysmal element may be judged by the extent of the blood pressure rise caused by histamine. The relative importance of the sustained hypertensive element may be judged by the extent to which the blood pressure is lowered by 933F.

hormone is no longer necessary to maintain hypertension and another mechanism has developed in response to the continued release of the amines. Or perhaps this group represents the normal occurrence of essential hypertension in a group of individuals. Fig 111 diagrammatically represents the present concept. The disease may be present in any stage and remain there or progress to another variety. It is clear that many tumours are present for a considerable time for calcification

in degenerated *in situ* in the tumour have been reported. It would therefore seem reasonable to take the view that the patient's symptoms might change as the secretory activity of the tumour altered. It would also seem reasonable to associate a sustained hypertension to a continuous release of adrenaline and noradrenaline although it is possible that other activities stimulated by transient discharge of medullary hormone for example pituitary ACTH might cause the sustained hypertension. This possibility is supported by the occasional finding of a slow fall in blood pressure lasting several days after removal of the tumour.

In the metabolic group less information of day to day changes is available but it seems clear that a mechanism exists in which transient hormone liberation results in sustained endocrine changes. Further speculation on this aspect is not warranted in our present state of knowledge.

#### THE DIAGNOSIS OF PHAECHROMOCYTOMA

The ultimate diagnosis of the condition depends either upon the anatomical localization of its presence or on the demonstration of circulating adrenaline and noradrenaline. The discussion of the anatomical localization is not our purpose here suffice to say that in the case of small tumours it is difficult if not impossible and that a number of unsuspected tumours have been discovered at operation or post mortem. The demonstration of excess medullary hormone may be achieved either directly in blood or urine or by producing effects which only occur in association with a biologically active tumour. The demonstration of an excess of adrenaline or noradrenaline in blood is not always feasible but the amounts excreted in the urine can be estimated (Engel and Euler 1950). These workers demonstrated a great increase in the urine content of adrenaline and noradrenaline in two patients with phaeochromocytoma and also found a good correlation between the relative preponderance of either amine in the urine with the concentration in the tumour.

The pharmacological tests which seek to demonstrate specific effects due to circulating medullary hormones are more complex. The first group are those which produce a paroxysmal discharge of medullary hormone of which the best

known is the histamine test of Roth and Hyak (1945). An intravenous injection of 0.5 mg histamine is given to the patient. If a phaeochromocytoma is present there is a brisk rise in blood pressure often to extreme limits with associated symptoms similar to those experienced during the paroxysmal attacks. It is clear that this test will be of greatest use in the patients in Group I and the accuracy will decrease in Group III. Indeed a moderate rise of blood pressure sometimes follows an intravenous histamine in essential hypertension and therefore the interpretation of this test may be difficult. A positive response to the histamine test is a rise in blood pressure greater than the response to the cold pressor test. Histamine probably acts by a direct stimulation of the cells of the adrenal medulla and not by a reflex. In normals only small amounts of hormone are liberated insufficient to cause much effect but with phaeochromocytoma large amounts enter the circulation. A number of other substances also cause transient liberation of pressor hormones from the adrenals. These are adequately considered in the clinical literature.

The second group of pharmacological substances are those which modify the action of adrenaline or noradrenaline. Of these the most important is 933F (piperidyl methylbenzodioxane). In 1947 Goldenberg, Snyder and Aranow demonstrated a fall in blood pressure in patients with phaeochromocytoma following injection of 0.25 mg 933F per kilogram body weight. In patients with essential hypertension this amount of adrenergic blocking agent caused either no change or a rise in blood pressure. Goldenberg and Aranow (1950) were able to report 59 positive (vaso depressor), no false positive and 3 false negative responses to this test. Clearly on clinical grounds the 933F test is of value in the diagnosis of phaeochromocytoma. But a negative response will be observed if the test is carried out in patients who are non hypertensive or if the hypertension is due to permanent vascular change.

Although of great clinical value the physiological basis of this test is complex and requires further elucidation. In an earlier chapter we discussed the observations of Prunty and Swan (1950) who were unable to obtain a fall in blood pressure on injection of 933F in normal subjects rendered hypertensive by means of a continuous infusion of adrenaline. We wonder



whether the dose of  $^{131}\text{I}$  given to humans by the intravenous route is sufficient to produce true adrenergic blockade. In general the duration of the adrenergic blocking action of  $^{131}\text{I}$  is much less than the reported period of hypotension following its administration to patients suffering from phaeochromocytoma.

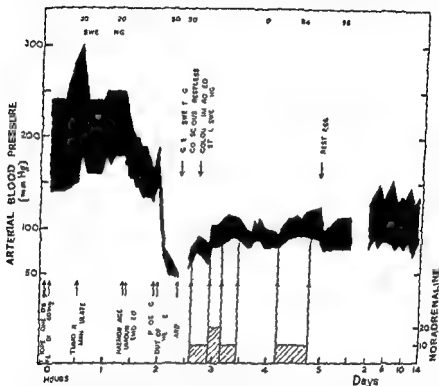


Fig. 11. The arterial blood pressure during and after the surgical removal of a phaeochromocytoma.

The hatched squares indicate the rate of administration of L noradrenaline intravenously in  $\mu\text{g}$  per minute. After 30 minutes the infusion of noradrenaline was replaced by one of saline, but as the systolic pressure fell below 100 mm Hg the noradrenaline was restarted. After a further infusion of noradrenaline for 3 minutes the pressure remained at a satisfactory level (Swan 1951a).

The treatment of this condition is the surgical removal of the tumour. In most cases this is technically easy—but care must be taken to avoid or combat a post-operative hypotensive state which frequently develops. Fig. 11.2 shows the changes in blood pressure in a 42-year-old man during and after surgical

removal of a phaeochromocytoma (Swan 1951a) In this patient an infusion of noradrenaline was used to maintain the blood pressure In this case there had been sustained hypertension of 10 years standing and the tumour contained more than 90 per cent noradrenaline It was considered that the noradrenaline acted as a temporary replacement of the tumour secretion which had been so acutely removed Not all patients in hypotension respond to medication as favourably as the case just mentioned Indeed several cases have been reported in which the hypotension was unaffected by heroic efforts at medication This is probably due to a condition analogous to the adrenaline shock described by Vigran and Essex (1949) In an attempt to avoid this fatal complication Cahill and Monteith (1951) used dibenamine in two cases before operation with a favourable result

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## CHAPTER 12

### THE VASO VAGAL SYNDROME

It will be remembered that Barcroft Edholm McMichael and Sharpey Schafer showed that the vasomotor centre could excite active vasodilatation in skeletal muscle during fainting (Chapter 2). Other circulatory changes taking place in this curious and common circulatory mishap will be described in this chapter.

Michael Foster (1888) believed that fainting was a form of cardiac syncope due to vagal inhibition of the heart. The output, arterial blood pressure and cerebral blood flow dwindled and consciousness was lost. In World War I Lewis (Cotton and Lewis 1918, Lewis 1932) questioned this. In the dog Starling had shown that vagal inhibition comparable with that in fainting did not materially diminish the arterial blood pressure. Increase in stroke volume compensated for decreased rate. Neither was there hypotension in heartblock though the heart rate was halved. Lewis concluded that the fall in blood pressure must be due to peripheral vasodilatation. To confirm this he atropinized subjects who had just fainted. The bradycardia was abolished but the blood pressure fall persisted. He introduced the term vaso-vagal syndrome to emphasize that both vagal inhibition and peripheral vasodilatation were among the physiological changes taking place in the faint.

Soma Weiss, Wilkins and Haynes (1937) and Wilkins, Haynes and Weiss (1937) induced faints for the purpose of investigation. This they did by oral administration of sodium nitrite followed by tilting upright. They confirmed that the fall in blood pressure persisted after atropinization and concluded likewise that it was due to peripheral vasodilatation. Their concept of the nature of the dilatation differed from Lewis's. Lewis seems to have considered it as being arteriolar causing decrease in resistance and so fall in pressure. They thought it was venous causing decrease in the effective blood volume and so decrease in output. During collapse in the upright position they sometimes recorded negative venous

pressures at heart level. They thought that the arterioles were constricted since the blood flow in the hand decreased to zero. But they observed that the circulation in the legs was not much changed since the oxygen saturation of the femoral venous blood remained normal (their table shows an increase).

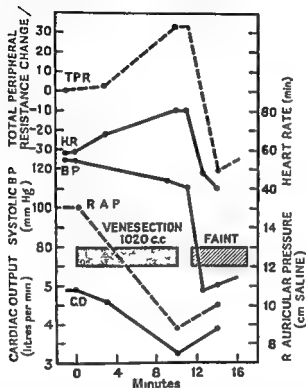


Fig 12.1 Result obtained by McMichael and Sharpey Schafer in an experiment on a Female Ambulance Unit Volunteer showing that fainting is not a form of cardiac syncope.

During the faint in this subject the cardiac output actually increased (Barcroft, Edholm, McMichael and Sharpey Schafer 1944).

McMichael and Sharpey Schafer (Barcroft, Edholm, McMichael and Sharpey Schafer 1944) were the first actually to measure the right auricular pressure and cardiac output by cardiac catheterization during the faint. Neither changed appreciably as shown in Fig 12.1. Their findings have since been confirmed by Warren, Brannon, Stead and Merrill (1945).

and by Wood and Burchell (1950). Fainting was not a form of cardiac syncope. The abrupt fall in blood pressure was due to decrease in peripheral resistance.

In the same investigation at the British Postgraduate Medical School peripheral vasodilatation was found in the skeletal muscles and later shown to be of nervous origin (Chapter 2). In connection with this Sharpey Schafer found an apt observation of John Hunter's (1793). 'I bled a lady but she fainted and while she continued in the fit the colour of the blood that came from the vein was a fine scarlet.' Commenting on this before the publication of our results McDowall (1938) thought it signified muscle vasodilatation. Increased muscle blood flow during fainting probably also explains the rise in brachial venous pressure previously observed by Ershler, Kossman and White (1943).

The question arises as to whether this vasodilatation in muscle also occurs in fainting due to causes other than haemorrhage. Is it really part of the vaso vagal syndrome? Emotional fainting is the commonest manifestation of the syndrome, but here one is up against the difficulty of inducing a subject to faint from emotion while his forearm is in a plethysmograph. However, during an experiment one of Sharpey Schafer's subjects did faint spontaneously and increase in forearm blood flow was recorded (Brigden, Howarth and Sharpey Schafer 1950). This was confirmed by Greenfield (1951). A preclinical student who fainted at the sight of blood offered to act as subject. But in the experiment when shown a syringe of blood he did not do so. As he and Greenfield were anxious for a faint Greenfield put the blood in a beaker and asked him to drink it. This was successful and the fall in blood pressure, bradycardia and increase in forearm blood flow seen in Fig. 12.2 were recorded.

Besides emotional fainting there are other causes as for example anoxia. Schneider (1918) found that subjects rendered unconscious by oxygen lack fell into one of two groups: non fainters and fainters. In World War II Anderson, Allen, Barcroft, Edholm and Manning (1946) investigated the effect upon the forearm blood flow of breathing oxygen-nitrogen mixtures calculated to provide oxygen tensions equivalent to heights of between 18 000 and 24 000 feet. At

the time consciousness was lost the circulation of four fifths of the subjects was in the hyperdynamic state their carotids were pulsating vigorously and there was tachycardia and increased arterial blood pressure they corresponded to Schneider's non fainters. However about one fifth the fainters had typical vaso-vagal syndromes including

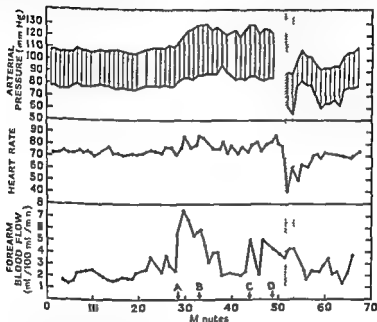


Fig. 1. Experiment showing that vasodilatation in muscle occurs in fainting induced by emotion. Circulatory changes during emotional fainting were prepared by watching a non-punctured needle in the arm. D: 10 ml of blood. The stippling represents loss of consciousness. In spite of the extensive fall in the arterial pressure during the faint the forearm blood flow remained relatively good (Gwenfeldt 1911).

increase in forearm blood flow (Fig. 12.3). Briden Howarth and Sharpey Schafer (1930) recorded increases in forearm blood flow in faints induced by tilting spinal anaesthesia and other means. They concluded that muscle vasodilatation was an essential part of the vaso-vagal syndrome.

Another important question is whether the fall in blood pressure is entirely due to vasodilatation in muscle or whether

vasodilatation elsewhere is partly responsible. Fortunately we now know what happens in the circulation through the liver, kidneys and brain. The effect on the liver blood flow was studied by Bearn, Billing, Ldholm and Sherlock (1951) in eight

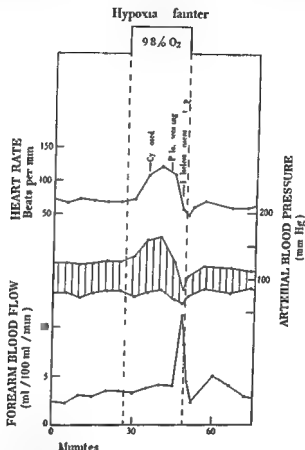


Fig. 12.3 Results showing that vaso dilatation in muscle occurred in faint induced by breathing 9.8 per cent O<sub>2</sub>. (Anderson, Allen, Barcroft, Edholm and Manning 1946)

subjects. The liver flow was measured by the bromsulphalein (BSP) method (Bradley et al. 1945). The principle of this is as described in Chapter 9. Bearn et al.'s results show that during fainting hepatic blood flow decreased on the average to about half its normal rate. As the decrease in the blood pressure was relatively more there is probably some vaso

dilatation in the splanchnic area. Crayson and Swan (1940) showed by a qualitative method decrease in blood flow in fainting in the colonic mucosa. de Wardener and McDewney (1951) studied the renal blood flow by observations on the clearance of para-aminohippuric acid (PAH). During the faint kidney blood flow decreased on the average to about three quarters of its normal rate. As in the case of the liver there was a relatively greater decrease of arterial blood pressure and probably some renal vasodilatation.

Lennox Gibbs and Gibbs (1935) studied the cerebral circulation by two methods. The first was by means of a heated thermojunction placed in the internal jugular vein the temperature of the junction being an inverse function of the rate of the blood flow. The second by measurement of the oxygen saturation of the internal jugular venous blood. The results of both methods leave no doubt that the cerebral flow decreases during the faint.

To return to the question of the extent to which the blood pressure fall in vaso-vagal attacks is attributable to vasodilatation in muscle. The circulation through the liver, kidneys, skeletal muscles and brain accounts for about four fifths of the total cardiac output. During the faint the flow through the muscles is doubled but that through the other principal organs is decreased. The vasodilatation in muscles is far greater than that elsewhere. In as much as vasodilatation does take place in the splanchnic area and kidneys it must be in part accountable for the blood pressure fall.

It is worth considering whether dilatation in the coronaries could contribute significantly to the fall in peripheral resistance. The resting flow amounts only to about 200 ml a minute (from Bing et al. 1949) but in exercise it may be 3 litres (Hill 1926). It has not been measured in the faint. It seems unlikely that there would be much vasodilatation. Probably the most important factor controlling the coronary flow is the metabolism of the heart. Since in the faint heart rate and arterial blood pressure are decreased so very likely are cardiac metabolism and coronary flow. Electrocardiographs taken during the syndrome show no sign of anoxia of the heart muscle (Weiss et al. 1937).

Vasodilatation in another small part of the peripheral



vascular system the finger tips was recorded plethysmographically by Rushmer (1944). As the skin in the front is pale and the blood flow in the hand diminished (Chapter 2) this may signify some release of constrictor tone in the abundant arteriovenous anastomoses in the finger tips.

Some further points are of interest. As the sympathetic nervous system mediates the vasodilatation in skeletal muscle (Chapter 2) it probably does so in the splanchnic area and kidneys. The corollary of this is that there should be no vasodilatation or fall in blood pressure in faints in totally sympathectomized subjects. In fact totally sympathectomized subjects are very apt to faint when they stand upright. The cause of these 'faints' needs further investigation. Maybe the hypotension is due to pooling of blood in the lower part of the body and consequent decrease of right auricular pressure and cardiac output which cannot be compensated for by splanchnic vasoconstriction.

Recent work suggests that hormones may play a part in the changes occurring in fainting. Brun, Knudsen and Raaschou (1945) noticed that the vaso-vagal attacks induced by tilting were followed by pronounced oliguria. They suggested that the cause was secretion of antidiuretic hormone by the pituitary. This was upheld by certain experiments. Diuresis in a waterloaded normal subject was inhibited by blood transfusion from one in the postsyncopal state. The changes in the chloride in the urine resembled those found after injection of pituitary extract and postsyncopal oliguria was much less in two patients suffering from diabetes insipidus. Taylor and Noble (1950) recovered from postsyncopal urinaemia after posterior pituitary like antidiuretic substance. Sterd, Hunkel and Weiss (1939) and Sumihara, Duncanson and Edholm (1949) found that injection of posterior pituitary extract in normal subjects caused nausea, abdominal discomfort, ashen pallor and headache. Pitressin secretion in the faint probably explains the persistence of pallor and splanchnic vasoconstriction for so long after the return of the blood pressure to normal (Bearn et al. 1951). The possibility of suprarenal secretion must be considered too since it might explain the output of liver glucose and muscle lactic acid (Bearn et al.). Now that a method of urine analysis is available for detecting increase in

blood catechol derivatives it would be interesting to apply it to postsyncopeal urine (Euler and Hellner 1950)

How is fainting caused? Lewis (1932) noted the resemblance of the vaso vagal changes to those of carotid sinus stimulation in animals (Heymans and Bouckaert 1928) and in sensitive human beings (Danielopolu 1929 see also Weiss and Baker 1933). He thought that they were caused by the same centres in the brain excited by the higher centres or by unknown afferent paths. Weiss, Wilkins and Haynes (1937) thought that vaso vagal attacks caused by nitrite and tilting were due to cerebral anoxia but this cannot be so. Breathing nitrogen (Lennox, Gibbs and Gibbs 1935) or air diluted with nitrogen (Anderson et al 1946) so as deliberately to produce anoxia of the brain beyond the point of unconsciousness does not as a rule cause fainting. How does nitrite and tilting induce fainting? Bridgen, Howarth and Sharpey Schafer (1950) have shown that tilting lowers the right auricular pressure. Lowering of the right auricular pressure is caused by other procedures which induce fainting. For example by haemorrhage (Bridgen et al), spinal anaesthesia (Bridgen et al), the post exertional state (Mateeff 1937), Eichna, Howarth and Bean (1947) and by forcible compression of the chest during full inspiration followed by sudden release (Lennox et al 1937). In these cases fainting is probably induced as Sharpey Schafer once suggested by stimulation of unknown sensory receptors in the cardio pulmonary system or great veins. Recent work by Pearce and Whitteridge (1951) and by Dawes and Mott (1950) emphasizes the possibility of a reflex from these areas.

It is not yet known whether pituitary secretion precedes the onset of fainting. If so it may help to precipitate the faint. Stead, Kunkel and Weiss (1939) found that intramuscular injection of pitressin induced fainting in two out of six subjects in the upright position. They thought that it caused pooling of blood in the lower part of the body. Rutherford, Godfrey and Griffiths (1941) have since found that pitressin decreases the circulating blood volume. These remarks on the cause of fainting show that it is still far from being understood.

Lennox, Gibbs and Gibbs (1935) were interested in the question of why fainters lose consciousness. They noticed as did

Weiss and Baker (1933) that pressure on the carotid sinus sometimes caused loss of consciousness but no fall in blood pressure. The loss of consciousness was caused by a neural mechanism. They wondered whether in fainting loss of consciousness was due to fall in blood pressure and cerebral anoxia. They found that during the faint the oxygen saturation of the arterial blood was almost normal 92 per cent but that of the internal jugular venous blood was only 20 per cent (normally 56 per cent). This was explained by the decreased cerebral blood flow. As reduction of the internal jugular venous oxygen saturation to below 30 per cent by breathing nitrogen invariably caused unconsciousness they thought that unconsciousness during the vaso vagal syndrome was usually caused by anoxia. However they could not say whether it was due to the direct effect of anoxia on the cells responsible for the conscious state or to stimulation of a neural mechanism.

It remains to draw attention to some other vascular conditions remarkably like fainting.

The first of these is the action of apomorphine reported from Innsbruck in a series of papers by Jarisch and his colleagues (Cowan 1943 Gsell 1943 Wothe 1943 Schneider 1943 Ehlich and Wallisch 1943 Bertolini and Jarisch 1944 Seidel 1945 Jarisch 1948). Subcutaneous injections of 10 mg cause lassitude yawning sweating salivation pallor nausea vomiting and often unconsciousness. Defaecation occurs occasionally. Breathing is not affected. Tachycardia is soon followed by marked bradycardia and precipitate fall in blood pressure as shown in Fig. 124.

Jarisch and his colleagues thought that the blood pressure fall was due to peripheral vasodilatation as it persisted after restoration of the heart rate by atropine. There were signs of vasodilatation. Though the skin was deadly pale the hands were warm and digital temperature often rose conspicuously. Owing they thought to dilatation of the A V anastomoses. The oxygen saturation of the brachial venous blood was increased and it sometimes became bright red. They recalled John Hunter's observation on the lady who fainted during blood letting. Owing to the resemblance of the changes to those of carotid sinus and depressor nerve stimulation they thought that the dilatation was mainly in the hepatic and

splenic blood reservoirs (Koch 1931) and in the skeletal muscles (Jarisch 192a)

Examination of the electrocardiogram of these subjects showed no impairment of the heart

They thought that the apomorphine acted directly by stimulation first of the sympathetic and then of the parasympathetic centre. As unconsciousness sometimes supervened when the blood pressure was normal they believed it excited Hess's

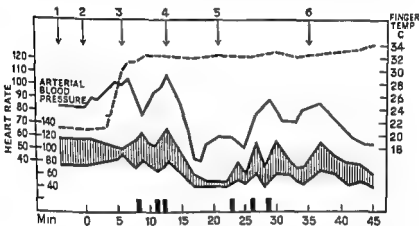


Fig 14 Experiment showing the likeness of the effects of apomorphine to those of the vaso vagal syndrome

The intracranial pressure falls in blood pressure and vasodilatation in muscle as shown by a fall in the oxygen saturation of the venous blood from the arm vein

1 Oxygen saturation per cent 10 mg apomorphine 3 Yawning feeling of fatigue 4 and 5 Oxygen saturation 49 and 50 per cent respectively Vomiting as denoted by the solid rectangle (Ehlert and Wallisch 1943)

(1929) sleeping centre. As yet there have been no measurements of cardiac output forearm blood flow or urinary anti diuretic substance after apomorphine

Vaso vagal attacks very like faints occur in the anaesthetized cat. Jarisch (1941) noticed that every now and again at the beginning of an experiment the blood pressure fell spontaneously and abruptly to about half its initial value and at the same time the heart slowed. Recovery usually occurred in a few minutes. Altogether he recorded 41 attacks which occurred in 10 per cent of his experiments. They took place

during chloralosepernocton but not during ether or urethane anaesthesia or in decerebrate animals. They invariably happened in the first ten minutes of an experiment and never except in one cat more than once. They seemed to be related to the entry into the circulation of sodium citrate during the preparation for recording the blood pressure with the mercury manometer. The fall in blood pressure was not abolished by atropine. The pulmonary arterial pressure fell, superior vena caval and right ventricular pressures remained constant or rose, the volume of the spleen increased. The phenomenon

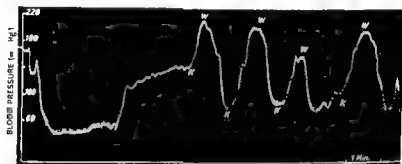


Fig 12.5 Precipitate fall in arterial blood pressure recorded by Jarisch during a vaso vagal syndrome in the chloralosed cat

Since the vaso vagal phenomena were abolished by cooling the vagi they were believed to have been triggered by afferent sensory impulses from the heart.

A vag cooled B warmed (Jarisch 1941)

reminded Jarisch of the Bezold effect (Jarisch 1940). He thought that the blood pressure fall and bradycardia might be due to excitation by the sodium citrate in susceptible cats of sensory receptors in the heart. In the Bezold effect cooling the vagi abolishes the fall in pressure and bradycardia due to stimulation of these receptors by veratrine. Cooling the vagi in these vaso vagal attacks also usually terminated the attack. This is shown in Fig 12.5. In one case the attack persisted due to continued spontaneous activity of the centres.

Konzett and Rothlin (1951) have confirmed Jarisch's observations and recorded decreases in the volumes of the gut and kidney. They added the very interesting observation that intravenous injections of adrenaline sometimes induce vaso vagal attacks by stimulation of the Bezold receptors.

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## APPENDIX

### PLETHYSMOGRAPHY

This appendix is intended for those who are unfamiliar with the plethysmographic method and is divided into two parts. A few historical notes form the first part; the second contains a short general description of the experimental procedure.

#### HISTORICAL NOTES

Apparatus for determining a change in the volume of an organ was in use in the seventeenth century. Borelli held the view that during contraction a muscle became inflated. Francis Glisson (1677) confronted this with a single experiment. In his book *de Ventrículo* he says:

But indeed this explosion and inflation of spirits has now for some time past been silenced, convicted by the following experiment. Take an oblong glass tube of suitable capacity and shape. Fit into the top of its side near its mouth another small tube like a funnel. Let a strong muscular man insert into the mouth of the larger tube the whole of his bared arm, and secure the mouth of the tube all round to the humerus with bandages so that no water can escape from the tube. Then pour water through the funnel until the whole of the larger tube is completely filled, and some water rises up into the funnel. Thus being done, now tell the man alternately to contract powerfully and to relax the muscles of his arm. It will be seen that when the muscles are contracted the water in the tube of the funnel sinks, rising again when relaxation takes place. From which it is clear that muscles are not inflated or swollen at the time that they are contracting, but on the contrary are lessened, shrunk and subsided. For if they were inflated the water in the tubule so far from sinking would rise. From this therefore we may infer that the fibres are shortened by an intrinsic vital movement and have no need of any abundant afflux of spirits either animal or vital, by which they are inflated and being so shortened carry out the movements ordered by the brain.

Some ingenious experiments leading, Jan Swammerdam to the same conclusion are shown in Fig. Ap 1 (Johnston 1940).

In 1828 Poiseuille applied the principle to the study of the circulation. He was interested in the change in diameter of an artery caused by the heart beat. Thus he was able to measure by observing



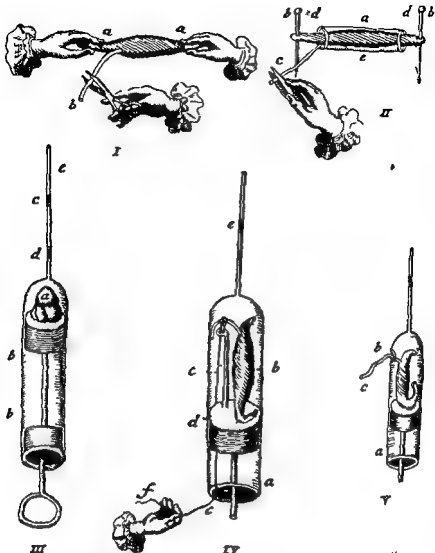


Fig Ap 1 A reproduction from Boerhaave's *Biblia Naturae* showing illustrations of the plethysmographs used by Jan Swammerdam

The text is a literal translation from part of the original text to this figure  
 I Muscle movement in the frog aa the muscle tends to grasp by the fingers b when the hanging nerve is touched the muscle contraction draws the hands together II Method showing thickening of muscle during contraction in glass tube through which muscle is drawn bb needle transpiercing tendons c the nerve touched dd displacement of needle bb contracting muscle fills up centre of glass tube III Method showing that the heart occupies less space in contraction a contracting heart is placed upon piston of glass tube bb glass tube c water droplet introduced into tube of siphon descends with heart contraction d place in tube showing distance moved by droplet during time of descent IV Method showing that contracted muscle takes up less space a tube b muscle c silver thread through loop of which the nerve is passed d copper thread e silver loop at top through which silver thread is drawn c water droplet in siphon tube f hand stimulating nerve muscle contracts and droplet descends a little V Another method of showing the above a glass siphon b aperture drilled in the siphon c nerve drawn through the aperture (Johnston 1940)

the movements of a column of water in a graduated vertical glass tube communicating with a watertight chamber which contained a segment of a large artery.

The same principle was employed by *Picqu* in 1846 and independently by *Chelius* in 1850 to study circulatory and respiratory volume changes in the human limbs. The first instrument to record volume changes graphically which could therefore be truly said to have been a plethysmograph (*πληθισμογράφος* a filling and *γραφειν* record) was described by *Burson* in 1862. Details of the well known *Moroso* plethysmograph in use in 1875 are shown in Fig. Ap 2 (*Luciani* 1911).

In 1905 *Brodie* and *Russell* discovered that the plethysmograph could be used to determine the rate of the blood flow through an organ. This discovery had such far reaching results that it is best described in the authors own words. *Brodie* and *Russell* say

Most valuable information is to be gained by the plethysmograph as ordinarily applied but it gives only qualitative results which moreover in many cases are difficult to interpret. During the past three years we have applied a simple modification to the plethysmographic method which enables us to determine the rate of flow quantitatively with considerable accuracy. In principle this consists of blocking the vein of an organ enclosed within the plethysmograph for a short interval of time. The whole of the venous blood is thus retained in the plethysmograph and leads to a rise of the lever of the recorder. If the recorder be calibrated the rate at which the lever rises enables us to determine the rate of blood flow into the vein. In applying such a method as this it is obviously essential that the blockage of the vein must not be maintained so long as to impede the flow through the capillaries. Under all ordinary conditions the veins are never completely filled so that it is possible to store up in them a small extra quantity of blood without checking the inflow into them from the capillaries [omission].

The danger that the artificial venous obstruction may be checking the capillary inflow is easily guarded against by noting whether the lever of the recorder continues to rise at a uniform rate during the whole period of observation. Should this not be the case but the tracing become concave to the zero abscissa line the clamping is being maintained too long a time and the observation must be discarded.

We have controlled the method by comparing it with observations upon the rate of venous outflow as conducted in the experiments of *Burcroft* and *Brodie* upon the kidney the only modifications we have introduced being to record the rate of flow

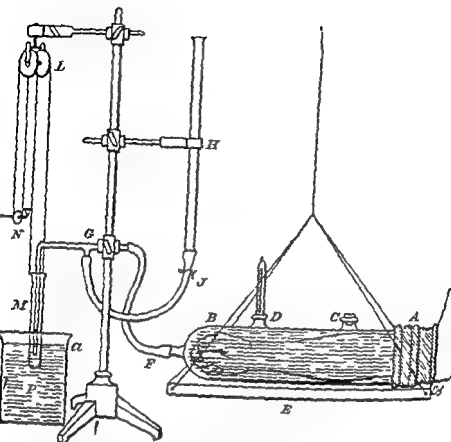


Fig. Ap. Moscos plethysmograph for recording slow variations in volume of vessels of forearm (diagram)

A glass cylinder to receive the forearm closed by rubber land this rests in the board *E* which is suspended from the ceiling by a wire *C* opening closed with a cork through which the cylinder can be filled with lukewarm water *D* opening through which a thermometer is placed showing temperature of water *F* tube through which the cylinder containing the forearm communicates with the small cylinder *M* which floats above the level of the fluid *a b* contained in large vessel *P* *N* lead weight carrying the pen to write on moving cylinder of kymograph which counterpoise *M* with which it is connected by two silk threads passing over the double pulley *L* *H* *J* burette that can be raised or lowered in a sling or changing the water in the float. The instrument works as follows: when the vessels of the forearm contract an amount of water corresponding with the diminution in volume is aspirated from the float *M* to the cylinder *A* this raises the float and depresses the counterpoise *N* which records the diminution of volume on the revolving cylinder. When on the contrary the vessels of the forearm dilate a quantity of water in the cylinder *A* is driven out into *M* so that it sinks and *N* is raised recording the increase of volume. To avoid positive or negative pressure above the forearm immersed in the cylinder *A* *B* care must be taken that its upper level is at the same level *a b* as the water contained in the receiver *P* where *M* is floating. (Lancet 1911)

from the vein in lead of turning it by a stop watch. We have found that the two methods give nearly identical results.

The method is applicable to all organs which can be inserted into an oncometer provided that the vein can be clamped within the oncometer. It is also applicable to a limb for the venous outflow can be blocked there by a circular ligature applied with so much



Fig. Ap 3. Thomas Gregor Brodie, F.R.S.  
The original was kindly loaned by the Royal Society.

force as to compress the veins without interfering with the arterial inflow.

In 1900 Brodie held no fewer than three posts in London: Professor Superintendent at the Brown Institution; Professor of Physiology at the Royal Veterinary College; and Lecturer in Physiology at the London School of Medicine for Women. His portrait is shown in Fig. Ap 3. It is not clear where he and Russell

performed the experiments referred to in their paper. Nor is it known whether they actually recorded the rate of the blood flow in a human limb though their words suggest that they did so.

Brodie and Russell remark that the plethysmograph could be used to determine the blood flow in a human limb was followed up by Hewlett and van Zwaluwenburg in 1909. The hand, forearm and elbow were enclosed in their instrument. Compression of the veins without interference with the arterial inflow was achieved by the use of a narrow pneumatic cuff placed on the upper arm. Their observations were made with the plethysmograph filled with air and they noted that the rate of the circulation was profoundly affected by fluctuations in the temperature.

To avoid errors due to temperature fluctuations and those due to movements of the limb in and out of the Mosco type of plethysmograph used by Hewlett and van Zwaluwenburg, Lewis and Grant in 1925 devised the type of plethysmograph shown in Fig. Ap 4. It enclosed a segment of the forearm and contained water to maintain the temperature constant.

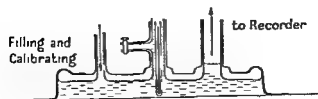
The first plethysmograph to be used for the determination of the rate of the blood flow in the hand was described by Freeman (1931). A simple form of hand plethysmograph is shown in Fig. Ap 5.

Three years later Grant and Pearson (1938) showed that what was measured by the hand plethysmograph was for the most part the circulation through the skin and what was measured by the forearm plethysmograph was mainly the blood flow through the skeletal muscles. The value of the plethysmograph for the determination of muscle blood flow was improved by placing it on the upper fleshy part of the forearm and by arresting the circulation at the wrist to prevent the entry of venous blood returning from the hand.

### EXPERIMENTAL PROCEDURE

This may conveniently be described by considering an experiment in which the effect of some procedure is to be tested on the rate of the circulation in the right hand and in the left forearm.

Room temperature is kept constant at  $20^{\circ}\text{C} \pm 1$  and entry of persons during the experiment is discouraged. Fig. Ap 6 shows a general view of the subject and plethysmographs. The subject is on a comfortable rubber mattress on a narrow table, his head supported and his body covered with a single blanket. The left hand is covered with a rubber surgical glove (Kerslake 1949) several sizes too large which is stuck round the wrist to the edge of a hole in a  $\frac{1}{4}$  in. thick soft rubber diaphragm. The diaphragm fits the wrist snugly—but not tightly, for venous congestion must be



ARM

Fig A14 Low and Grant plethysmograph for the forearm

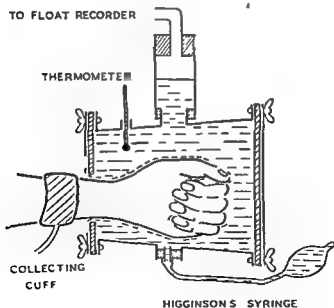


Fig A15 A simple form of plethysmograph for the hand  
The hand is placed in a loose fitting surgical rubber glove (R F W. elan  
MD. Thes. Belfast)

avoided. By means of wing nuts and two semicircular metal plates the periphery of the diaphragm is bolted firmly to a 2 in. wide flange on the end of the plethysmograph. The plethysmograph contains water up to the lower part of the vertical glass tube. The weight of the water presses the glove everywhere against the hand. From time to time the water is agitated by squeezing a bulb communicating with the interior of the plethysmograph and its exterior is heated with a small flame to keep the temperature at 32° C. The plethysmograph is mounted on a retort stand placed on a small table beside the subject, its height = such as to ensure that the veins of



Fig. Ap 6 Photograph showing plethysmographs on the right hand and the left forearm

the hand are collapsed (Cooper Cross Greenfield Hamilton and Scarborough 1949). The elbow = slightly bent to prevent the communication of respiratory movements to the hand and rests on a comfortable pillow. A narrow pneumatic cuff surrounds the wrist and = held lightly but firmly in position by a crepe bandage.

The same principles apply to the plethysmograph on the other arm. The upper part of the forearm is covered with a loose sleeve (Krogh Landis and Turner 1932; Grant and Pearson 1938) of thin latex rubber fixed at each end round a suitably shaped central hole in a soft rubber diaphragm. The temperature of the water for the forearm is kept at 34–35° C (Barcroft and Edholm 1943,

1946) The collecting cuff is placed just above the elbow and the arresting cuff on the wrist. Both are held in position by crepe bandages. (This is a convenient point to note that a more even constant temperature is maintained in electrically heated thermo

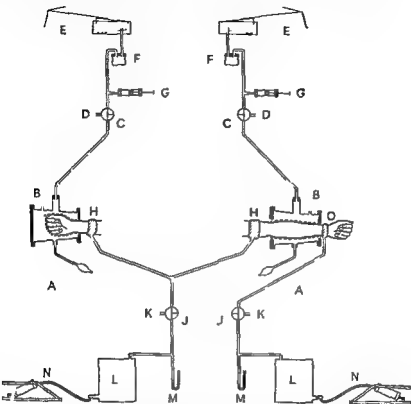


Fig Ap 7 Diagram of apparatus for recording the rate of arterial inflow into the right hand and left forearm

AA plethysmographs (thermometers not shown) BB vertical glass tubes CC three way glass taps DD side tube minimum ating with room air EE float orders FF trap GC syringes HH O pneumatic cuffs JJ three way glass taps KK side tubes communicating with room air LL reservoirs for compressed air MM mercury manometer NN foot pump

statically controlled plethysmographs which on the other hand are more bulky and must be very carefully made to avoid danger of electrocution (Abramson 1944)

The recording apparatus and arrangements for inflating the cuffs are shown diagrammatically in Fig Ap 7. Each plethysmograph



A A is connected through a vertical glass tube B B to a wide bore three way glass tap C C by means of which it can be put in communication with the room through a side tube D D or with a float recorder E E. Reflux of water from the recorder into the tubing is prevented by a small trap F F. The level of the writing point can be adjusted by means of a syringe G G. The two collecting cuffs H H are connected to a wide bore three way tap J by means of which they can be put in communication with the room through the side tube K or with a reservoir of compressed air L. The pressure of the air is shown by a mercury manometer M and maintained at 60-70 mm Hg by a foot pump N. The arresting cuff O is connected to a second similar set of apparatus J K L M N with the difference that the air in the reservoir L is maintained at a pressure of 200 mm Hg.

All four taps C C J J and both syringes G G are mounted on a board on the kymograph table with the foot pump readily accessible below. Before beginning recording the writing points are adjusted one above the other on the smoked kymograph paper and horizontal base lines are drawn round the paper.

To obtain simultaneous tracings of the rates of the arterial inflow into the hand and into the forearm the procedure is as follows. The air pressure in the reservoirs is checked. The taps are turned to put the plethysmographs in communication with the recorders. As the recorders are apt to stick when empty some air is introduced by means of the syringes so that the writing points are raised a little above the base lines. Tap H is then turned to arrest the circulation distal to the forearm plethysmograph. Three quarters of a minute later the kymograph is started the switch also turns on a light illuminating a notice in front of the subject with the words 'keep quite still and look at this light'. One minute after arresting the circulation in the hand (Karslake 1948 Rodd 1951) tap F is turned to inflate both collecting cuffs simultaneously. The water level in the vertical glass tubes begins to rise air is displaced into the recorders and the arterial inflow curves are inscribed. After 10 sec. of venous compression the kymograph is stopped and the taps turned to put the plethysmographs and cuffs in communication with the room air.

At the beginning of the experiment tracings of the arterial inflow are generally recorded at 5 min. intervals for  $\frac{1}{2}$  or  $\frac{1}{4}$  an hour to confirm that the circulation has reached a steady state. The effect of some procedure is then tested. If a rapid alteration in the rate of the circulation is anticipated inflow curves may be recorded at more frequent intervals. For this purpose the collecting pressure is applied for about 5 sec. at the beginning of each  $\frac{1}{4}$  or  $\frac{1}{2}$  min.

interval the circulation in the hand remaining arrested and the drum continuing in motion

At the end of the experiment each recorder is calibrated by introducing a known volume of air into the system with the syringe. The distance travelled by the recording paper in 1 min is marked

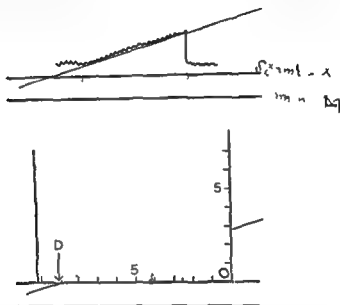


Fig Ap 8 Procedure for calculating the rate of the blood flow from the tracing

Top Inflow curve with sloping line drawn and continued through horizontal base line

Bottom Use of graph paper ruled in centimetres and millimetres to read off the rate of the blood flow directly in ml/100 ml limb/min. Lower edge of paper on base line with mark D at point of intersection of sloping line. Centimetre scale up right hand side. Sloping line intersects at 3 cm which is also the rate of the blood flow in ml/100 ml tissue/min

upon it and the volumes of the portions of the hand and forearm enclosed in the plethysmographs measured by water displacement

The rates of the blood flow are then calculated from the curves traced on the kymograph paper. Sloping lines are drawn through the inflow curves to cut the base line as shown in Fig Ap 8. The experiment constant  $D$  is obtained from formula

$$D = \frac{V \times V}{A} \quad \frac{M}{X \times V}$$

where  $\lambda$  is the vertical distance travelled by the recorder writing point for 1 ml increment of content

$l$  is the volume of the hand in hundreds of millilitres

$M$  is the distance in centimetres travelled by the kymograph paper in 1 min

A piece of graph paper ruled in centimetres and millimetres is trimmed square and a mark made at the bottom edge  $D$  cm from the right hand corner as shown in Fig Ap 8. A centimetre scale is marked along the edge of the right hand side with the zero at the right hand bottom corner. The rates of the blood flow are now read off the kymograph paper. The graph paper is placed with the bottom edge touching the horizontal base line the mark  $D$  coinciding with the point where the base line is intersected by a sloping line. The distance from the right hand bottom corner of the graph paper up the right hand side to the point of intersection of this sloping line is read off on the centimetre scale. The figure obtained is that for the rate of the blood flow expressed in millilitres per 100 ml hand per minute. The rates of blood flow in the hand are read off from the other inflow curves in a similar way. To obtain those for the forearm the values of  $\lambda$  and  $l$  being different a new value of  $D$  must first be found from the formula—

The method has the advantage that once the value of  $D$  has been obtained the rates of the blood flow for all the inflow curves for a part can be quickly read off without any further arithmetic. The basis for this graphic method is as follows

Let  $\lambda$ ,  $M$  and  $l$  be defined as above

$D$  be any given distance in centimetres travelled by the drum paper

$I$  be the upward movement of the writing point in centimetres while the paper goes  $D$  cm

$F$  be the rate of the blood flow in ml 100 ml tissue/min

Then

$$F = \frac{LM}{\lambda I} \quad 1$$

In any given experiment  $\lambda$ ,  $M$  and  $l$  are constant. A distance  $D$  can therefore be chosen so that

$$\frac{DM}{\lambda I} = 1$$

Substituting this in equation 1

$$F = \frac{LM}{\lambda I} \times \frac{\lambda I}{M}$$

or

$$F = L$$

That is the rate of the blood flow in ml/100 ml tissue/min is equal to the upward movement of the writing point in centimetres.

Similar principles apply to the method of measuring the rates of the blood flow in the calf of the leg and in the foot.

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